A CRITICAL EXPLORATION INTO MANITOBA'S HIV CARE CASCADE

by

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Abstract

Increasingly over the past decade, research has sought to describe and better understand patterns of engagement in the continuum of health care services for people living with human immunodeficiency virus (HIV), and to identify factors that shape engagement. The HIV care cascade was developed as a framework to examine and monitor engagement across sequential stages of the continuum of HIV care, from HIV acquisition to virologic suppression. In Manitoba, data describing the epidemiological trends of HIV and the delivery and utilization of relevant services is scarce. As a result, local understandings of engagement in HIV care are limited. Together, the three studies compiled in this dissertation offer a foundation upon which to expand upon and provide nuance to our current knowledge of HIV epidemiology and HIV-related service coverage in Manitoba. This was specifically achieved through the expansion of local data infrastructure for doing HIV research and programming and the use of an HIV care cascade framework to better conceptualize and understand HIV clinical epidemiology and related health services within the province.

First, this work describes the establishment of the first prospective clinical cohort of people living with HIV and receiving HIV care in Manitoba, which was strategically created as an embedded research component of the Manitoba HIV Program. Individual-level clinical data from cohort participants are anonymously linked to relevant provincial administrative health databases. Using these linked data, multiple sets of HIV care cascade indicator definitions were developed through an iterative consultation process with local experts in HIV care, resulting in a final cascade model including the most programmatically relevant indicator definitions and locally relevant estimates. Finally, equity analyses were performed using care cascade data,

disaggregated by key demographic and socioeconomic variables. Equiplots were used to visualize absolute inequalities among groups of cohort participants across the cascade steps and multivariable logistic regression models assessed statistical significance of observed inequalities.

Expanding local data infrastructure through the development of the first clinical cohort of people living with HIV in Manitoba afforded important opportunities for addressing critical research, programming, and policy questions. Using cohort data to develop a locally relevant HIV care cascade model revealed promising patterns of engagement in HIV care in the province, while highlighting key points of disengagement across the cascade. In particular, individuals living with HIV who are younger, non-white, or have a history of injecting drugs are less likely to be optimally engaged in care in Manitoba. Together, the bodies of work in this dissertation generated evidence, knowledge, and specific tools that can be used to further our understanding of the most effective ways to optimize coverage of HIV care in Manitoba and work towards achieving equity in the health and well-being of people living with HIV in the province.

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The work presented in this dissertation was conducted on Treaty 1 Territory, and the Manitoba HIV Program has clinic sites on Treaty 1 and Treaty 2 Territories. These are the original territories of the Anishinaabeg, Cree, Oji-Cree, Dakota, and Dene peoples and the homeland of the Métis Nation—all of whom have called this land home since a time long-preceding the arrival of settlers, like me.

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List of Abbreviations

ABBREVIATION	DEFINITION
95%CI	95% confidence interval
Ab	Antibody
AIDS	Acquired Immunodeficiency Syndrome
AOR	Adjusted odds ratio
ART	Combination antiretroviral therapy
CAD	Coronary artery disease
CGPH	Centre for Global Public Health, Department of Community Health Sciences, University of Manitoba
CIHR	Canadian Institutes of Health Research
COPD	Chronic obstructive pulmonary disease
CPL	Cadham Provincial Laboratory
CSDH	Commission on the Social Determinants of Health
DM2	Type 2 diabetes mellitus
DPIN	Drug Program Information Network
EMR	Electronic medical records
HCV	Hepatitis C virus
HIPC	Health Information Privacy Committee of Manitoba Health, Seniors and Active Living
HIV	Human immunodeficiency virus
HTN	Hypertension
ICD-9/10	International classification of diseases, ninth/tenth revision
IDU	Injection drug use
IGPH	Institute for Global Public Health, University of Manitoba
IMA	Information Management & Analytics group of Manitoba Health, Seniors and Active Living
IQR	Interquartile range
LHIV	The "Advancing Primary Health Care for Persons Living with HIV in Canada" study

ABBREVIATION	DEFINITION
MAI	*Mycobacterium avium-intracellulare*
MCHP	Manitoba Centre for Health Policy
MDGs	Millennium Development Goals
MHSAL	Manitoba Health, Seniors and Active Living
MSM	Men who have sex with men, condomless anal sex between men
NIR	No identified risk
OIs	Opportunistic infections
OR	Odds ratio
PCMH	Patient-centred medical home
PHDL	Public Health Data Laboratory of the Institute for Global Public Health
PHIN	Personal Health Information Number
PJP	*Pneumocystis jirovecii* pneumonia
RNA	Ribonucleic acid
SD	Standard deviation
SDGs	Sustainable Development Goals
SEFI-2	Socioeconomic Factor Index-Version 2
SES	Socioeconomic status
STBBIs	Sexually transmitted and blood-borne infections
STIs	Sexually transmitted infections
UM-HREB	University of Manitoba Health Research Ethics Board
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
US CDC	United States Centers for Disease Control and Prevention
VPN	Virtual Private Network
WHO	World Health Organization

Chapter 1. Introduction

1.1 Background

Over the past decade, increased emphasis has been placed on describing and understanding the continuum of health care services involved in the diagnosis, treatment, and care of people living with human immunodeficiency virus (HIV) in a given setting [1-3]. The HIV care cascade was developed as a framework to examine and monitor the sequential stages of the continuum of HIV care through which people living with HIV would ideally progress in a clinical setting [1, 3, 4]. In its simplest form, the HIV care cascade comprises a series of five sequential steps that track the proportion of individuals living with HIV who have: (i) been diagnosed, (ii) been linked to HIV care, (iii) been retained in care, (iv) initiated HIV treatment with combination antiretroviral therapy (ART), and (v) reached virologic suppression [1, 2, 4, 5]. Over time, conceptualizations of the HIV care cascade have evolved to reflect real world complexities in providing and receiving HIV care [3, 6-13]. Importantly, this framework allows for the identification of points along the continuum at which gaps, “leakages”, and/or bottlenecks exist, thus impeding individual-level progression toward the clinical goals of treatment initiation and virologic suppression [1, 2, 14]. The HIV care cascade is also regularly used as a tool to monitor the performance of programs or health systems providing HIV treatment and care services [2, 4, 5, 15, 16]. Ultimately, analyses using the HIV care cascade framework have the potential to provide critical information for the development of interventions, programs, and policies for improving and optimising the delivery and uptake of HIV-related care services.

1.1.1 HIV in Canada and Manitoba

The Public Health Agency of Canada (PHAC) estimates that as of the end of 2018, 88,881 people have been diagnosed with HIV in Canada since 1985 [17], and it has been estimated that over one-fifth of people living with HIV in Canada at any given time are unaware of their HIV status [18]. The number of new HIV diagnoses reported to PHAC[i] has been relatively stable over time, with 2,561 new cases reported in 2018 [17] and a national diagnosis rate of 6.9 per 100,000 population [17]. Over the past few decades, the complexity and heterogeneity of Canada's HIV epidemic has become increasingly clear. Nationally, HIV disproportionately burdens Indigenous populations (First Nations, Métis, and Inuit) and people who have immigrated from "HIV-endemic"[ii] countries [17, 19-22]. The greatest proportion of new HIV infections in Canada were attributed to condomless anal sex between men, followed by condomless vaginal (heterosexual) sex—41.4% and 32.3%, respectively, in 2018 [17]. Meanwhile, geographic variation within Canada's HIV epidemic is also evident, with

[i] Since 2000, HIV has been classified as a nationally notifiable disease in Canada (https://diseases.canada.ca/notifiable/diseases-list). Each jurisdiction is required to report all confirmed cases of HIV to PHAC on an annual basis.

[ii] As defined by PHAC (https://www.canada.ca/en/public-health/services/hiv-aids/publications/epi-updates/chapter-13-hiv-aids-canada-among-people-from-countries-hiv-endemic.html)

Saskatchewan, Québec, Manitoba, and Ontario experiencing average annual rates of new infections higher than the national average [17].

Manitoba has among the highest number of new HIV infections per 100,000 population in the country, consistently above the annual national average [17, 21, 22]. In 2018, Manitoba Health, Seniors and Active Living (MHSAL), estimated that 1,572 people were living with HIV in the province (personal communication, J. Paul, 16 April 2020). Despite this, aside from the national HIV surveillance data provided by PHAC and annual epidemiology and surveillance reports published by MHSAL, relatively little is known about HIV epidemiology in the province. Based on provincial surveillance data, it is clear that injection drug use (33.9%), condomless sex between men (24.4%), and condomless vaginal sex (20.9%) were the most commonly identified HIV risk exposures in Manitoba in 2018 [23]. Furthermore, in 2018, when compared to national incidence data, new HIV infections in Manitoba were disproportionately high among Indigenous people (50% vs. 19.3%) and females (40% vs. 29.3%) [17, 24]. When disaggregated further, we see that new infections among females in Manitoba are largely attributed to injection drug use (37.2%), whereas the majority of new infections among males are attributed to sexual acquisition (condomless sex between men, 29.7% and condomless heterosexual, 21.9%) [24]. Additionally, heterogeneity in rates of new HIV infection exists across the province by geography, age and sex [24]—77.6% of new diagnoses in 2018 occurred in Winnipeg, and among females who were newly diagnosed in 2018, 11.6% were ≤19 years (compared to 1.6% of males) and 14.0% were ≥60 years (compared to 3.1% among males) [24].

Data on the delivery and utilization of HIV care services in Manitoba is also scarce. However, each year, the Manitoba HIV Program—the primary provider of HIV care in the province—publishes reports that provide additional information, beyond the scope of MHSAL

reports, about the clinical characteristics and treatment outcomes of clients newly entering care in the province. Of particular note is the remarkably large proportion of people who enter care at a relatively late stage of infection, with CD4 counts ≤350 cells/mm3. Fortunately, the proportion of clients who presented late to care has been consistently decreasing in Manitoba [23, 25-27], ranging from 55.9% in 2016 [26] to 34.2% in 2018 [23]. Late presentation to care has important clinical implications, being significantly associated with increased mortality, comorbid opportunistic infections and forward transmission [28-30], as well as economic implications for local health systems [31]. In Manitoba, the proportion of clients entering care off-treatment—many of whom have been newly diagnosed with HIV—with an unsuppressed viral load (≥200 copies HIV RNA/mL) has been consistently greater than 90% over the same time period [23, 25-27]. Mitigating the potential seriousness of these numbers is the high rate of treatment initiation within a year of entering care with the Manitoba HIV Program [23, 25-27]. Given these statistics, it is critical to examine and describe the complex contextual factors that shape the lives of people living with HIV in the province, including their ability and/or likelihood to access and utilize HIV-specific health services.

1.1.2 Provincial strategies to address HIV in Manitoba

In 2015, MHSAL outlined a clear five-year strategy to address sexually transmitted and blood-borne infections (STBBIs), including HIV, across the province [32], which includes promoting healthy sexuality and harm reduction practices; enhancing treatment, management, and support services for those infected with STBBIs; strengthening existing STBBI surveillance and reporting efforts; and supporting and furthering STBBI-focused research in the province. In order to reach their vision of "preventing and minimizing the impact of [STBBIs] on Manitobans" [33](p. 12), MHSAL explicitly acknowledges the necessity of intersectoral co-

operation and incorporating of the principles of diversity, cultural safety, and health equity, into their strategic plan [33].

A detailed understanding of the HIV care cascade and current health outcomes of Manitobans living with HIV will be important for informing future STBBI strategies and to optimize the configuration of health services and policies that will support the continued improvement in health outcomes for Manitobans living with HIV. Currently, one major obstacle to Manitoba's progress is the distinct lack of literature examining care pathways for people living with HIV in the province. Becker and colleagues [28] have called for more research in Manitoba to "develop approaches to facilitate earlier HIV diagnosis, linkage and engagement in care" (p. 22). Additionally, the World Health Organization (WHO) has specifically emphasized the importance of social science and implementation research to better assess and understand how people living with HIV interact with existing health care programs and their experiences of barriers and facilitators in receiving HIV-related services [15].

1.2 Rationale for presented work

This dissertation comprises three studies that, together, aim to address limitations in the academic literature and to fill gaps in our knowledge and understanding of HIV epidemiology, care delivery and utilization, care pathways, and outcomes for people living with HIV in Manitoba [28]. Up to now, publicly available HIV epidemiological data in Manitoba are limited to annual surveillance reports published by PHAC [17] and MHSAL [24]. These reports provide comprehensive, descriptive analyses of the previous year's new HIV infections but are unable to provide insight into patterns and trends in care, service delivery and uptake, or clinical outcomes for people living with HIV in the province.

In 2013, Manitoba received funding through a Canadian Institutes of Health Research (CIHR)-funded multisite program of research, entitled *Advancing Primary Health Care for Persons Living with HIV in Canada* (the LHIV study), to establish a prospective clinical cohort of people living with HIV in Manitoba. This study presented an opportunity to develop the first comprehensive source of de-identified, individual-level, HIV-specific health data in Manitoba and to use these data to begin to address key knowledge gaps in local HIV epidemiology—including patterns of healthcare utilization and relevant clinical outcomes—and to understand healthcare needs of people living with HIV in the province. Similar cohorts have been developed and are now are well-established in other Canadian provinces, including British Columbia [34] and Ontario [35].

To inform policies around the provision of HIV care services to people living in Manitoba, and to improve the design and delivery of services within the Manitoba HIV Program, research focusing on the strengths and weaknesses of our current system of HIV care and support is crucial. As such, the studies contained within this dissertation aimed to conduct foundational work that will begin to characterize how people living with HIV receive and engage with care and progress along a continuum of HIV care in Manitoba. This dissertation employs an HIV care cascade framework to critically examine the epidemiology of HIV in Manitoba, characterize progress along the continuum of HIV care for Manitobans, and better understand inequalities in clinical care and outcomes among people living with HIV in the province.

1.3 Literature review

1.3.1 Development and evolution of the HIV care cascade

The HIV care cascade ("the cascade") is a framework developed to examine and monitor individuals' engagement in, and utilization of, a continuum of HIV-related health services and

outcomes—including HIV testing, linkage to appropriate health services, and ultimately, initiation of effective treatment with ART—in the context of a particular health system. The cascade has also proven to be a useful tool for monitoring the performance of health systems with respect to the provision of HIV treatment and care services [30, 36-38] and monitoring HIV treatment and care programs, more specifically, as a way to identify gaps, bottlenecks, or limitations that exist within these programs [4, 5, 15, 16].

Many iterations of the HIV care cascade have been developed [1, 4, 7, 14, 39], all with the primary purpose of illustrating the "ideal", albeit often over-simplified, care pathway followed by people living with HIV, beginning from acquisition through viral load suppression. However, clinicians and other health service providers encounter a multitude of challenges while providing HIV-related health services to their clients, and individuals living with HIV are faced with numerous challenges to remaining engaged in HIV care that jeopardize their opportunities to achieve and maintain viral load suppression and other desirable health outcomes [13, 40-42]. As such, using the HIV care cascade to better understand how people living with HIV are moving through "stages" of HIV care is one way to identify, and subsequently address, these challenges in providing HIV-specific health services. More recent research has highlighted the inherent complexities of the cascade [7, 39, 42-45], and newer schematics have been developed to illustrate the potential trajectories followed by individuals who deviate from the "ideal" linear pathway towards viral load suppression [7, 44-47]. Given the heterogeneity of the HIV epidemic across Canada [17], understanding what an HIV care cascade looks like in different contexts, and for different populations within a given context, is essential in ensuring that the implementation of local HIV health services and clinical HIV care programs are effective and appropriately tailored to the needs of the targeted populations.

It is now important to critically appraise different approaches to utilising and describing the cascade, keeping in mind the models' potential programmatic utility. One of the first introductions to the care cascade was presented by Gardner and colleagues [1], who expanded upon a model of a continuum of engagement in HIV care—initially put forward by the U.S. Health Resources and Services Administration [48] and further described by Cheever [14]—to highlight the importance of continuity in HIV care. Importantly, while attempting to quantify the spectrum of engagement in HIV care and estimate the proportion of people living with undiagnosed HIV in the United States, Gardner and colleagues [1] were the first to depict the care cascade as a bar chart. This visual representation of the cascade comprises seven consecutive, discrete "steps"– HIV infected (undiagnosed), HIV diagnosed, linked to HIV care, retained in HIV care, need ART (that is, ART-indicated, according to relevant treatment guidelines)[iii], on ART, and ART-adherent/virologically suppressed— and set a precedent for future cascades. In fact, this depiction of the cascade is now employed as a standard tool by government agencies [2, 49] and leading organizations specialising in HIV prevention and care [5]. Many HIV care programs and health departments have also adopted the cascade to monitor and evaluate HIV prevention and care programs in their respective jurisdictions [40, 42].

[iii] After Gardner and colleagues published this original model, in 2015, the World Health Organization has moved to a "treat-all" recommendation, which suggests that all people living with HIV should initiate treatment as soon as possible. AS such, the "need ART" step is often excluded from modern cascade models. (https://www.who.int/mediacentre/news/releases/2015/hiv-treat-all-recommendation/en/).

Importantly, in 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) introduced its 90-90-90 strategy to see the "end of the AIDS epidemic by 2030" [50], which includes targets that "address progress along the HIV cascade of engagement in care, [and measures] the degree to which programs are meeting their ultimate goal of viral suppression" [50]. Specifically, the UNAIDS global HIV targets state that by 2020, 90% of all people living with HIV will know their status, 90% of those diagnosed will be on sustained ART, and 90% of those on treatment will have reached viral suppression [50]. One year later, the 90-90-90 initiative was followed-up by the UNAIDS 95-95-95 Fast-Track Targets [51], which suggested that progress should be further expedited to achieve, by 2030, (i) fewer than 200,000 new HIV infections per year globally; (ii) "zero [HIV-related] discrimination" (p. 11), with particular emphasis on key vulnerable groups; and (iii) all 90-90-90 targets increased to 95% [51]. Given that the 90-90-90 targets and the 95-95-95 Fast-Track targets mirror the steps of the HIV care cascade, it was—and still is—anticipated that they would prove be important tools for HIV care programs, globally [52]. However, despite the excitement around the 90-90-90 initiative in Canada [49, 53, 54], and globally [55-60], numerous challenges exist before these lofty goals are realized [37, 61-65].

1.3.2 Programmatic uses and applications of the cascade

Since the HIV care cascade was first conceived, and as prevention and care programs have begun to realize its potential programmatic utility, a number of limitations to the cascade have been highlighted. Specifically, researchers have noted the intensive data requirements to develop and maintain a programmatically useful HIV care cascade [4, 7, 37, 39, 45-47, 66-71], and there are numerous challenges in designing context-specific cascades that adequately capture complexities within HIV care trajectories [4, 7, 42, 47, 67, 72]. As such, a number of modified

cascade models have been proposed to accommodate for these and other intricacies that are overlooked in more "traditional" cascades [for example, see 7, 45, 47, 67].

One of the most commonly identified limitations of traditional cascade models—for example, those put forward by Nosyk and colleagues [4] and Gardner and colleagues [1]—is the problematic assumption that progression through the cascade (from HIV infection through viral load suppression) is a linear, uninterrupted process [3, 7, 42, 47, 73]. This oversimplified interpretation of the cascade ignores complexities involved in HIV care [42], and does not account for the movement of individuals into and out of the discrete cascade steps [7]. Indeed, while Nosyk and colleagues [4] acknowledge that this idealized trajectory is not reflective of reality in most circumstances, their cascade, which is nearly identical to the cascade introduced by Gardner and colleagues [1], fails to adequately address this limitation. This oversimplification impedes the model's ability to provide useful insight into how to reconfigure HIV care programs in a way that would minimize leakage and attrition within the cascade. For example, without understanding reasons *why* some people living with HIV may not be adhering to their prescribed ART, programs would be unable to develop effective strategies or interventions to address an observed "leakage" at the *on treatment* step of the cascade. Similarly, Hallett and Eaton [47] acknowledge another limitation to the traditional conceptualization of the cascade in its inability to capture information about people who enter into the cascade at later steps, through so-called "side doors". Entry into the cascade through a side door occurs if, for example, someone is found to be HIV-positive late in their disease course, with a low CD4 count, and initiates ART without first being retained in "pre-ART" care [47].

Meanwhile, Powers and Miller [7] acknowledge some intrinsic strengths of the traditional cascade framework, including "its simplicity and intuitive format, as well as its flexibility in

describing different geographical regions, population subgroups, and service settings" [7], while also noting important limitations in its practical utility and interpretation. In particular, the authors also problematize the assumption of "unidirectional flow" through the cascade, the lack of specificity around "the disposition of those who are 'lost' at each juncture [between cascade steps]" [7] and, similar to Hallett and Eaton [47], the lack of clarity around how individuals may re-enter the cascade after being lost to care. To address these shortcomings, the authors developed the HIV States and Transitions framework, which more explicitly describes "the states that [people living with HIV] may be in and the transitions among these states" [7]. The major strength of the States and Transitions framework over previous cascade models is its ability to clearly track individuals' forward and backward movement along the cascade—a process known as "cascade churn" [9, 11, 74, 75]. To do this, the authors propose a cascade framework that includes—similarly to more traditional conceptualizations of the cascade—a set of discrete states (cascade steps) into which a population of people living with HIV can be organized to provide a cross-sectional snapshot of the local epidemic. However, the States and Transitions framework [7] differs from traditional models because:

> the proposed schema requires that the fundamental set of aggregation categories are exhaustive and mutually exclusive, and it explicitly lays out the multidirectional pathways that HIV-infected persons can follow in moving from one category to another. (p. 342)

Another important feature that distinguishes the States and Transitions framework from previous cascades is that it clearly differentiates between individuals who are in a State for the first time, and those who have re-entered the State. As a result, the framework is also able to capture the rates at which individuals transition between different states, or steps, of the cascade, thus allowing this model to be much more effective at tracking and characterising churn [7].

Recently, McNairy and colleagues [67] published an article proposing another variation on the traditional HIV care cascade, which incorporates a more rigorous examination of clinical outcomes at each step of the cascade as a way to evaluate quality of care within HIV care programs. Conventionally, viral load suppression is the primary (or only) outcome of interest related to the HIV care cascade—used both as an indicator of disease progression [76-78] and to estimate the probability of forward HIV transmission [79, 80]. McNairy and colleagues [67] critique the heavy focus on viral load suppression in traditional cascade models, suggesting that it ignores the progress and well-being of the relatively large proportion of people living with HIV who have not, for a variety of reasons, initiated ART. In response, the authors put forward the "comprehensive HIV care cascade" [67], which places focus on clinical outcomes of people living with HIV, regardless of their treatment status (that is, pre-ART or on ART), as a way to follow care trajectories and account for all individuals who enter into the cascade. The authors assert that the comprehensive cascade addresses known gaps in existing cascade models and is an "important tool that complements the traditional HIV treatment cascade to evaluate HIV program performance, at the health facility, across health facilities, or at regional or country levels" [67]. To use the comprehensive cascade as a tool for the evaluation of HIV care programs, relevant clinical outcomes for all individuals in care would be measured at pre-determined time points after entry into HIV care—for example, three, six, and twelve months post-entry. At each time point, clinical outcomes for all clients in care with the program would be assessed and classified as optimal, suboptimal, or poor, depending on the step of the cascade they reside at the time. The authors provide an example of quality of care indicators for an individual in pre-ART care as follows: retention in pre-ART care with known ART ineligibility is classified as an optimal outcome, retention in pre-ART care with known ART eligibility is a

suboptimal outcome, and loss to follow-up or death prior to ART initiation is classified as a poor outcome [67]. By incorporating assessments of patient outcomes at specific time points, the complementary cascade allows HIV care programs to keep track of clients' care trajectories at the individual and aggregate levels, while simultaneously evaluating program performance by determining the proportion of clients who experience optimal, suboptimal, or poor outcomes at various time points. Finally, the comprehensive cascade is unique in its incorporation of time as an integral component in the evaluation of HIV care, specifically allowing programs to be evaluated based on clients' timely progression through the HIV care cascade [67].

Finally, other researchers have highlighted another potentially important function of the cascade: to track HIV transmission. Skarbinski and colleagues [81] have shown through mathematical modelling that in 2009, the majority (91.5%) of HIV transmission in the United States occurred among individuals who were living with undiagnosed HIV and those who were diagnosed but not retained in care. While this finding is not especially surprising, it provides further evidence that expanded HIV testing and improved strategies to enhance engagement in the HIV care cascade are critical to stem HIV epidemics [81, 82]. Importantly, work presented by Skarbinski and colleagues [81] "turns the treatment cascade into an HIV prevention tool" [82]. Garnering information about risk of HIV transmission at different points along the cascade creates opportunities for developing context-specific interventions to strengthen local HIV

prevention efforts through improved testing, linkage, and retention in care [81, 83].[iv] Indeed, combining the "worlds" of HIV care and prevention through the cascade emphasizes the great potential held by the cascade, but may consequently challenge conventional notions of the roles and responsibilities of HIV care programs, placing more responsibility on care providers and administrators to expand their scope of practice to include HIV prevention [82].

Programmatically, capturing information about "unconventional"—although, arguably, more common [7, 42, 47]—patient trajectories in HIV care is an important way to inform optimal program design and service configuration that is able to accommodate patients' more complex care and support needs [47, 84]. Newer conceptualizations of the cascade that incorporate additional details about clients' care trajectories and elucidate reasons for leakage within the cascade are especially helpful to enhance the cascade's ability to inform HIV care program design and resource allocation. The "side door" cascade proposed by Hallett and Eaton [47], the HIV States and Transitions framework [7], and the comprehensive HIV care cascade [67] are all examples of cascade models that could provide programmatically relevant information to HIV care programs regarding client progression through the cascade. In particular, such models are likely to be highly beneficial for HIV care programs in terms of providing insight into how resources might be most effectively allocated to optimize health outcomes for those receiving HIV care services. However, the work involved in incorporating

[iv] For example, see the *Compendium of evidence-based interventions and best practices for HIV prevention*, compiled by the Centres for Disease Control and Prevention (http://www.cdc.gov/hiv/research/interventionresearch/compendium/lrc/index.html).

adequate complexity into a cascade, while remaining theoretically and programmatically relevant, is likely to pose a number of practical challenges for HIV care programs [4, 7, 37, 42, 45-47, 67, 72].

1.3.3 Engagement in HIV care as a complex, dynamic process

1.3.3.1 Understanding patient engagement across disciplines

Increasingly, biomedicine recognizes the importance of patient-centred care [85], and along with it, the concept of "patient engagement" has gained traction [86-88]. In general terms, patient engagement refers to the idea that individuals are critical stakeholders in their own health care—particularly in relation to chronic conditions. Furthermore, meaningful engagement, in which patients are actively involved in decision-making around their own care, can improve quality and safety of service delivery, produce better health outcomes, and improve overall patient satisfaction [86, 88]. Evidence suggests that collaborative models of care are a viable solution to minimising health care costs in the context of widespread austerity, globally [86]. Despite garnering increased attention and support, patient engagement remains poorly defined, with striking variation in meanings across disciplines [86]. Through a literature review, Barello and colleagues [86] found that within biomedical research, patient engagement was conceptualized as a top-down strategy in which a health care system "mobilizes" individuals to become actively involved in their own care and disease management through pedagogical efforts to improve health literacy and attitudes towards care. In contrast, the nursing literature conceptualizes patient engagement as a key component in understanding one's physical and emotional needs to inform the development of appropriate clinical and care interventions [86]. This is a more collaborative understanding of the term that views care providers, and particularly nurses, as facilitators to engagement who provide individual support and consider patients'

emotional status in the planning and development of individualized care plans. Somewhere in between the conceptualizations from biomedicine and nursing, literature from public health and health services research focuses on the influence of community and social context on patients' engagement in their care [86]. In this context, engagement is understood as a tool to aid the development of high-quality, collaborative care and prevention strategies that both improve the health of the public and reduce costs to the health care system.

In addition to identifying vast variability among definitions of patient engagement across disciplines, Barello and colleagues [86] note that the "on-going academic debate seems to focus principally on patient engagement's impact on clinical and economical outcomes, seeing patient engagement as a static rather than as a dynamic condition" (p. e20). This oversimplification, the authors argue, ignores multiple, complex factors that likely influence patterns of engagement over time [86]—a finding in common with much of the cascade literature [7, 47, 67]. Finally, the authors note that the academic literature is distinctly lacking holistic perspectives of engagement from patients, which is likely limiting the validity of any definitions of engagement that have been developed to date [86].

1.3.3.2 Defining and conceptualising engagement in HIV care

Patient engagement has also received significant attention in the context of HIV, particularly in relation to the care cascade [1, 3, 6, 8-10, 12-14, 44, 89-91]. Optimal engagement in HIV care affords numerous individual-level benefits to people living with HIV. Relative to sub-optimal engagement in HIV care, continuous engagement has been associated with decreases in incidence of morbidity and mortality [1, 3, 6, 8, 92-95] and more consistent adherence to ART regimens [3, 92, 95], leading to higher CD4 counts and decreased viral loads [3, 8, 95, 96], slower HIV disease progression [6, 96], and fewer occurrences of treatment failure due to viral

resistance [1, 3, 9]. Importantly, there are also public health benefits to continuous engagement in HIV care, namely a potential for reduction in HIV transmission [1, 3, 6, 8, 9, 81, 82, 96], which is due, in part, to higher rates of viral suppression and "safer" sex and injecting practices among people engaged in care [8]. Consequently, engagement in HIV care is also conceptualized as a crucial component of HIV prevention efforts [81, 82].

It is worth noting that in the cascade literature, engagement is often used interchangeably with "retention in care"—a measure that can be clearly defined based on missed and kept clinic visits or regularity of HIV-specific blood work, such as CD4 counts or viral load tests [9, 94, 96-98]. However, some literature differentiates engagement from retention in HIV care, describing engagement as a more comprehensive conceptualization of the dynamic relationships and processes involved as individuals move through the continuum of HIV care. For example, when Gardner and colleagues [1] and Cheever [14] describe engagement in relation to the HIV care cascade, it encompasses multiple steps of the cascade—linked to care, retained in care, and on treatment. The complex and dynamic nature of engagement in HIV care, relative to retention in care, is highlighted in more detail in a growing body of literature [3, 12, 91, 95]. Another important distinction is that retention is conventionally depicted as an outcome-oriented measure, whereas engagement is best understood through a process-oriented lens, as a spectrum that focuses on "dynamic and bidirectional relationships that exist between steps along the [cascade]" [3].

Another key consideration in the conceptualization of engagement in HIV care is cascade "churn" [3, 9-11]—an idea that specifically draws attention to complexities within the cascade. Though difficult to quantify, characterising cycles of engagement/re-engagement in care among people living with HIV is particularly important for understanding how to best utilize the cascade

for enhancing HIV treatment and care programming [7]. The term churn was originally used in the HIV care literature by Gill and Krentz [11] to describe the ways in which geographic mobility between HIV care centres in southern Alberta impacted care delivery, local prevention efforts, and resource allocation. However, as the care cascade gained momentum, the concept of churn has been expanded to describe "differing patterns of retention among different segments of the population over time" [10], or more generally, the cyclical process of engagement/re-engagement in HIV care over time [3, 9, 13, 42, 44, 96, 99]. Although the importance of acknowledging churn in HIV care is generally recognized, it is not a concept that is easily captured in the conventional, linear models of the HIV care cascade. Fortunately, some scholars—such as Powers and Miller [7] and Hallett and Eaton [47]—have managed to incorporate some aspects of churn into their cascade models and, as a result, are able to elucidate mechanisms through which cyclical processes of engagement/re-engagement impact outcomes and timely progression through the broader continuum of HIV care.

1.3.3.3 Factors impacting engagement in HIV care

A growing body of literature identifies specific factors that influence individuals' engagement in HIV care [1, 3, 6, 8, 10, 41, 44, 72, 90, 95, 96, 100, 101] and examines how suboptimal engagement may impact HIV-specific health outcomes [1, 3, 6, 8, 10, 83, 95, 96]. In the context of a multisite program focusing on providing services to enhance linkage, retention, and re-engagement in HIV care, Maulsby and colleagues [90] found that most participants who were sub-optimally engaged in their HIV care reported numerous unmet broader health and well-being needs—including housing, food, and employment—that, out of necessity, took precedence over accessing HIV health services. Indeed, numerous studies identify a variety of individual, social, and structural/systemic factors that acts as barriers to engagement in HIV care.

1.3.3.3.1 Individual level factors

At a broad level, evidence suggest that people who are younger, female, and/or identify as racial or ethnic minorities are more likely to be sub-optimally engaged in care [3, 6, 44, 72, 91, 95, 96, 100, 102]. Additional individual-level factors that have been associated with poor engagement in HIV care include problematic substance use [3, 6, 12, 41, 72, 90, 96, 100, 103], mental illness [3, 6, 8, 12, 72, 90, 96], and internalized stigma [8, 12, 96]. Both Colasanti and colleagues [96] and Christopolous and colleagues [12] found that newly diagnosed individuals often reported hesitancy to initiate treatment and/or attend clinic appointments because they did not want to be constantly reminded about their HIV status. Similarly, feeling "healthy" or asymptomatic is often associated with disengagement as the perceived need to attend frequent medical appointments and visits with providers is not as pressing [6, 8]. At the same time, experiencing improvements in personal biomedical HIV outcomes (that is, increased CD4 counts and/or reduced viral load) has been identified as a facilitator to continuous and regular engagement in care [12]. A number of studies have also identified associations between a person's psychological state at the time of their diagnosis and their likelihood to remain engaged in HIV care over time [8, 12, 95]. Additionally, a general fear of the unknown after receiving a positive diagnosis has been noted as a common barrier to engagement [8, 12, 72]. In particular, Flores and colleagues [8] noted that feelings of denial, shame, and shock upon diagnosis are often associated with patterns of relatively poor long-term engagement. Furthermore, through in-depth interviews with people diagnosed through routine HIV testing in San Francisco, Christopolous and colleagues [12] found that individuals who felt like active players in the management of their own HIV care, in partnership with their providers, were more likely to perceive their care as a central component to their overall well-being and, therefore, prioritized

active engagement in their HIV care—a finding corroborated by a lexicographic review by Barello and colleagues [86].

1.3.3.3.2 Interpersonal, social, and community-level factors

Many scholars have identified strong social support from friends and family as a key facilitator to engagement in HIV care [8, 72, 95, 96, 101, 104]. Additionally, the immense importance of a strong, trusting relationship between patient and provider was one of the most commonly cited factors that encourages and facilitates engagement in HIV care [6, 8, 12, 72, 91, 95, 105, 106]. Collaborative relationships in which clients are able to contribute to decisions around their care plans and providers valued and centred patients' experiences are noted to be particularly conducive to supporting long-term engagement in HIV care [8, 12]. Furthermore, individuals who do not disclose their HIV status, or have a negative experience with disclosing to family and/or others close to them, appear to be less likely to engage in HIV care [8, 96, 101, 106]. Stigma and discrimination are common experiences among people living with HIV and have a well-documented association with suboptimal engagement in care [1, 3, 8, 12, 72, 91, 101, 106]. In particular, negative interactions with health care providers that result in individuals feeling judged discourage engagement and, in fact, contribute to long-term disengagement among people living with HIV [8, 41, 106]. Importantly, both Christopolous and colleagues [12] and Kempf and colleagues [106] found that people who have been living with HIV for some time often empathized with their newly diagnosed peers and felt a sense of responsibility to act as "navigators" to help orient people to the health care system and HIV care, more specifically. Ultimately, the desire to set a "good example" for others in HIV care seems to strongly encourage long-term engagement [12, 106].

1.3.3.3.3 Structural and systemic factors

Structural and systemic factors are perhaps the most commonly cited barriers to continuous engagement in HIV care. Particularly, factors related to the health system and clinic structures, laws and policies pertaining to HIV, and other environmental factors impact people's ability or desire to engage in their HIV care. Many studies noted that an HIV clinic's location [8, 72, 91, 106] and hours of operation [6, 72, 91, 106], as well as flexibility of clinic appointments—that is, ability to easily cancel/reschedule on short notice [91, 106]—affected peoples' ability to optimally engage in their HIV care. Additionally, a lack of transportation or limited transportation options was one of the most commonly cited structural factors preventing optimal engagement in HIV care [6, 8, 12, 72, 91, 96, 106]. A few studies also highlighted the complexity of navigating the health care system—particularly for individuals who have had limited need to access health services prior to diagnosis—as a significant barrier to both linking to and remaining engaged in HIV care [8, 12, 41, 106]. Individuals who report financial troubles [1, 8, 41, 72, 91, 96, 106], unemployment [6, 91, 100, 107], a lack of health insurance [3, 6, 72, 91], unstable housing [3, 6, 96], and/or food insecurity [96] were also likely to have histories of sporadic or suboptimal engagement in HIV care. At a broader level, some studies note the role of existing laws and policies that criminalize HIV and/or behaviours associated with its transmission—such as injection drug use and sex work [8, 72]—in impacting people's ability to adequately engage in care. Individuals reporting histories of incarceration or legal troubles often experience sub-optimal engagement in their HIV care [12, 72, 100]. Importantly, racism and legacies of colonialism in health care systems and biomedicine, generally, impact engagement in HIV care [108-110]—for example, by manifesting as general distrust of the health care system and providers among people of colour [95, 109] and other marginalized groups [91].

Finally, and importantly, research shows that perceptions of what constitutes engagement in HIV care among people living with HIV differs from standard definitions developed by researchers and clinicians [6, 12]. Castel and colleagues [6] assert that because chronic comorbidities are common among people living with HIV, they are often engaging with the health care system regularly and able to obtain ART from other providers, even if they are not attending HIV-specific appointments and therefore do not meet standard definitions of "engaged in care". Furthermore, Christopolous and colleagues [12] noted that people living with HIV who were perceived to be out of care were "often unaware of provider-defined parameters for being 'in care' and at times did not realize that their status had changed to 'out of care'" (p. 229). As such, the authors call for further research to investigate discrepancies in definitions and understandings of "engagement" among different stakeholders [12].

1.3.4 Methods for building an HIV care cascade

As demonstrated by numerous scholars, each step of the HIV care cascade can be quantified for a given population, represented either as crude proportions of people estimated to be living or diagnosed with HIV, or as conditional proportions of people in the numerator of the previous cascade step [for example, see 4, 111, 112-116]. The utility of a cascade will differ depending on the type of data used to generate the model and how the data are analysed to generate each step. For instance, modelling the cascade data as proportions of the total number of individuals living with HIV can provide care providers and care program planners with estimates of the magnitude of the local HIV epidemic, and an idea about overall engagement at a population level, while cascades generated using conditional proportions of individuals in each cascade step can provide important information about "leakages" in the cascade and highlight potential points to focus efforts toward minimising gaps service provision. Before establishing

the best methods for developing a context-specific HIV care cascade, it is important to decide upon clear definitions for each cascade step indicator, and to consider all potential data sources for developing a comprehensive cascade for the given setting.

1.3.4.1 Defining and measuring steps of the HIV care cascade

One key advantage of the HIV care cascade is its ability to eloquently break down, into clear, discrete steps, the complex care pathways for people living with HIV—from HIV diagnosis to viral suppression and/or other clinical outcomes for those not on ART [46, 67]. Additionally, as the cascade becomes more widely used by HIV care programs globally, there is potential to be able to compare and contrast trends in HIV care across diverse contexts to assist in highlighting common obstacles that prevent timely progression through the cascade [39, 52, 66]. Furthermore, in the context of UNAIDS 90-90-90 Initiative, Lourenço and colleagues [66] emphasize the need to derive comparable global estimates for each indicator, which, the authors argue, will only be achievable with the implementation of standardized guidelines for the development of the HIV care cascade. In order to ensure cascade comparability, consistent and reproducible definitions of and methodologies for measuring each step of the cascade are necessary. With this in mind, a recent systematic review by Medland and colleagues [52] highlighted multiple differences in definitions, methodologies, and data sources used to generate estimates for each cascade step across multiple jurisdictions. The authors found particularly high variability among the methodologies used to estimate the first cascade step—total number of people living with HIV (diagnosed and undiagnosed) in a given jurisdiction—which ultimately led to significantly different estimates, as evidenced by studies from British Columbia and Australia [4, 52]. Because the first cascade step is the foundational denominator upon which subsequent indicators rely, Medland and colleagues [52] argue that this uncertainty has the

greatest potential to undermine cascade comparability and utility. Although, variation among definitions for the remaining cascade steps was minimal, the systematic review did identify a wide range of different data sources used to generate those estimates [52]. While the majority of reviewed studies used more than one population-based dataset to derive cascade estimates—for example, registries of all HIV diagnoses; central registries from mandatory reporting of HIV-specific blood work, such as CD4 counts and viral load tests; and/or population-based clinical data—the datasets themselves varied substantially across jurisdictions and geography, and data was often not available for the entire population. Based on findings from the review, Medland and colleagues [52] deduced that jurisdictions with mandatory reporting of HIV blood work or linked, population-based clinical databases generated the most comparable care cascades, but acknowledged that "implementation of these methods may be unfeasible outside smaller programs in wealthier jurisdictions" (p. 20640).

To further organize and categorize the kind of variability found within definitions and data sources used to develop HIV care cascades, Haber and colleagues [46] developed "typologies" for HIV care cascade models, based upon the scope and methodologies used to derive estimates for each step. When describing a cascade based on its scope, the authors [46] refer to both breadth and depth; where breadth refers to "the range of the cascade staging, from the event at which an individual enters the cascade to the final event ending the cascade achievement" (p. 104) and depth is "the number of stages [for example, HIV diagnosis, linkage to HIV care, etc.] between entry into the cascade and final cascade achievement" (p. 104). As such, a cascade with the widest possible breadth would range from time of HIV acquisition to death, whereas a deep cascade includes a greater number of discrete steps within the breadth of a given cascade. Haber and colleagues [46] also describe cascade typologies based upon the

measurements and methods employed to derive estimates for each cascade step. First, the authors delineate two types of cascades that differ based on the denominator measure used in each step. Denominator-denominator linked cascades use the same denominator (including the same individuals) for each step of the cascade (for example, estimated number of people living with HIV), while denominator-numerator linkage refers to cascades in which individuals are only eligible to be counted in the numerator of a step if they are also included in the denominator of the *same* step [46]. The authors assert that an ideal cascade should be both denominator-denominator and denominator-numerator linked. In this case, the denominator of each cascade step (except for the first step estimating the number of people living with HIV, diagnosed or not) would be the numerator of the preceding step, thus depicting a true (albeit simplified) continuum of care for a defined group of individuals. Next, Haber and colleagues [46] suggest that cascade models can also be classified on the basis of the population from which data are collected to generate cascade estimates—either a single population or multiple populations. The authors favour cascades that use data derived from a group of individuals that share common geographies, HIV exposure categories, or demographic characteristics, as pulling data from a single population "improves internal consistency and carries lower risk of biased inference regarding...transitions [between cascade steps]" [46]. Similarly, Miller, Lesko and Powers [42] suggest that the accuracy of cascade estimates could be improved if the population from which data are derived are carefully considered in the interpretation of the cascade. Finally, Haber and colleagues [46] detail their preference for developing care cascades using longitudinal rather than cross-sectional datasets, and have published multiple studies to illustrate the benefits of longitudinal data for cascade development [37, 68]. This preference is echoed, again, by José and colleagues in their study using longitudinal cohort data from the United Kingdom [45].

Longitudinal data is perceived to be superior because they incorporate less bias than cross-sectional data and they allow for survival analyses, which are important for tracking individuals' movement through the cascade while illuminating patterns of churn, delays, or timely progression between steps. Indeed, previous work has highlighted the need to place more emphasis on evaluating late entry into each cascade step [39], and, as previously mentioned, to better understand churn [3, 11, 42, 47]. While Haber and colleagues [46] note that an ideal cascade would always be "broader and deeper,... denominator-denominator link[ed], denominator-numerator link[ed], and ... based on a single population [with] longitudinal data" (p. 106), it is important to acknowledge that developing such a model may not be feasible in many settings, even those with relatively comprehensive health data systems in place. For circumstances in which the most rigorous methodologies may not be possible, Haber and colleagues [46] highlight a number of important strengths to a more straight-forward methodology using cross-sectional data; namely, its accessibility. Cross-sectional data collection and management is much less onerous, and simple analyses of the data produce cascade estimates that are easily understood by wide audiences. By creating these typologies, Haber and colleagues [46] distinguish different approaches that have been used to generate HIV care cascades in different contexts, and ultimately contribute to the growing body of literature dedicated to improving cascade utility and comparability.

1.3.4.2 Possible data sources to generate estimates for HIV care cascade steps

Intuitively, as HIV care cascade models become increasingly complex, so too will the data required to adequately estimate each cascade step. If we assume, as Haber and colleagues [37, 46, 68] and José and colleagues [45] suggest, that a longitudinal dataset, representative of a single population, is the ultimate source from which to derive data to generate cascade estimates,

then the resource most closely resembling this for most jurisdictions would be a population-based public health or HIV/AIDS surveillance database. Indeed, cascades developed in the Canadian [112, 117] and American [71, 114, 115] contexts have relied heavily on public health surveillance databases to develop their own cascade models. However, it is necessary to acknowledge limitations inherent to these data; for instance, surveillance databases are often rife with missing or inconsistent data, particularly when they rely upon collating HIV-specific indicators from jurisdictions that use different methodologies of data collection [71, 116]. As such, bringing multiple data sources together through triangulation is often the most effective strategy to develop cascade estimates albeit with certain, acceptable margins of error [71, 116, 118]. In fact, as the popularity of the cascade has grown, a number of groups have shown that individual-level public health surveillance and laboratory data [71, 116, 118, 119], clinical data from cohorts or administrative databases [52, 71, 118-120], health insurance programs [118], and in some cases, data from manual chart review or individual case investigation [116, 119], can be combined and used together to generate cascade estimates. Most often, these seemingly disparate cascade-relevant data sources can be linked to one another using unique, personal identifiers, which facilitates both denominator-denominator and numerator-denominator linkage [46], and thereby strengthens their ability to generate meaningful cascade estimates.

Another important consideration is the feasibility of developing cascades in settings with limited resources, where the rigorous data needs become prohibitive [37, 45, 52]—especially in terms of data infrastructure, cost, and/or human resources [4, 39, 67, 69]. As noted by many cascade researchers [for example, 4, 39, 67, 69], the availability of administrative health data, program data, and even clinical data is limited in many settings—particularly in low and middle income countries—and the ability to link health care utilization data to individual level outcomes

is even less common. Hladik and colleagues [69] propose that an alternative to using large, population-based datasets in countries with suboptimal data infrastructure is using population-based surveys to obtain data that can be used to generate cascade estimates. One benefit of this method is the ability to link survey data to biological samples—for example, HIV viral load data to estimate viral suppression within the study population—to complete the cascade [69]. Furthermore, in contexts where HIV epidemics are driven by transmission between and within key populations—for example, sex workers, "high risk" men who have sex with men, members of transgender communities, and/or people who inject drugs—complex sampling strategies used when implementing population-based surveys—such as respondent-driven or time-location cluster sampling—are better able to reach members of key populations and members of other groups who may not access HIV-related health services through conventional means (that is, through established clinics or health centres), or at all [69]. Importantly, Hladik and colleagues [69] also note a number of limitations to implementing large-scale surveys to collect cascade data. As with any methodology that depends upon self-reported data, surveys are inherently susceptible to biases. Questions inquiring about behaviours or practices that may directly influence HIV care outcomes, such as viral load suppression, may be perceived by survey participants as sensitive or stigmatising and are, therefore, particularly prone to reporting or social desirability biases [69]. Measurement errors may also arise due to recall bias if survey participants are unable to accurately recall historical HIV-specific health care events or appointments or if refusal rates for providing biological specimens are high. Furthermore, population-based surveys are resource intensive. The time, money, and human resources required to fully implement a survey that could act as a reliable data source for an HIV care cascade are substantial and must be considered carefully [69].

1.3.4.3 Consensus definitions for HIV care cascade steps

Although universal consensus has not been reached for definitions pertaining to each HIV care cascade step, a number of studies have consistently used similar definitions and procedures for generating cascade estimates. Nearly unanimously, back-calculation is used to estimate the total number of people living with (diagnosed and undiagnosed) HIV in a given jurisdiction [121]—though variability in specific methodologies can yield substantially different HIV prevalence estimates [52]. Similarly, the *diagnosed with HIV* step is consistently defined as any person who is alive in a given jurisdiction who has received a positive HIV diagnosis at some point [52]. Most often, the *linked to care* step has been defined in the literature as evidence of at least one encounter with an HIV-specific health care provider (a proxy measure is typically used, defined as evidence of a clinic appointment, a viral load test, or a CD4 count) within a selected time period post-diagnosis, commonly set to 90 days [3, 52, 71, 116, 119]. Definitions of *retained in care* are most varied in the literature, though two measures are quite common: one that simply measures retention in care and another that measures continuous retention [116, 118, 119]. Typically, someone is considered retained in care if there is evidence of at least one HIV-specific health care encounter in a one-year period [118], whereas continuous retention is most often defined as having evidence of at least two HIV-specific medical encounters, at least 90 days apart, within a one-year period [52, 71, 116, 118, 119]. However, this continues to be an active area of research, with increasingly more nuanced conceptualizations of the notion of retention emerging [89, 97, 122]. Finally, definitions for the last two cascade steps—*on treatment* and *virologically suppressed*—are fairly consistent in the literature [52]. An individual is typically considered to be *on treatment* if they have evidence of an active prescription or dispensation of an appropriate ART regimen [52, 116, 118], and *virologically suppressed* if the

last viral load in a given one-year period is suppressed (that is, <200 copies HIV RNA/mL) [52, 118, 123].

In 2013, the Surveillance and Epidemiology Division of PHAC convened a National HIV Cascade Working Group with the intention of developing a Canadian HIV care cascade using existing, available data from provincial and territorial jurisdictions [124]. The Working Group—which had representation from British Columbia, Alberta, Northwest Territories, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia, as well as from Correctional Service of Canada and PHAC—was tasked with developing standardized definitions for each cascade step. Through a consultation process spanning nearly three years, PHAC drew in expertise from clinicians, researchers, and representatives from provincial/regional public health units to identify existing data sources in each jurisdiction that could be used to measure cascade indicators. The Working Group acted as a forum in which open discussions took place regarding the limitations of available data within each jurisdiction, which were integral for informing the process through which consensuses were reached for cascade step definitions.

By mid-2016, the Working Group had developed primary and supplementary definitions for four of six steps of the HIV care cascade: linked to care, retained in care, on treatment, and suppressed viral load (see Table A.1 in Appendix A). Prior to convening the Working Group, PHAC had decided to rely on established methods for estimating the annual HIV incidence in each jurisdiction. Every three years, PHAC generates estimates for the number of people living with HIV in each jurisdiction using a number of complex methods including a workbook method, two statistical modelling methods, and an iterative spreadsheet model [125]. Indeed, the United States Centers for Disease Control and Prevention (US-CDC) has also recommended that independent jurisdictions do not undertake local estimations of undiagnosed HIV given the

complexity of the required methodologies and the intensive data requirements [71]. Additionally, as part of their annual reporting, the Surveillance and Epidemiology Division of PHAC develops estimates of new HIV diagnoses in each jurisdiction based on case reporting received from provinces and territories. For the sake of consistency, the Working Group agreed that those annual estimates would be used to represent the HIV diagnosed step of the national cascade [124].

While the purpose of the National HIV Cascade Working Group was to come up with definitions that could act as the "lowest common denominator" to which all jurisdictions could meaningfully contribute, a number of provinces, including Manitoba, routinely collect data that could lend itself to a more refined HIV care cascade, specific to their own province. As such, the Working Group developed primary indicators for a national HIV care cascade, to which all provinces and territories could contribute, in addition to more refined, supplementary indicators that had more robust data requirements (see Table A.1 in Appendix A). Importantly, for jurisdictions that have not yet formally established protocols to develop local cascade estimates, the PHAC consensus definitions developed through the work of the Working Group, provide a useful starting point upon which to base more sophisticated estimates.

Chapter 2. Conceptual Frameworks and Research Objectives

2.1 Conceptual frameworks and theoretical orientation

2.1.1 Inequities and inequalities in health

The WHO defines health inequity as the existence of "*avoidable* inequalities in health between groups of people within countries and between countries" [126]. According to the Commission on the Social Determinants of Health (CSDH) [127], health inequities are:

> caused by the unequal distribution of power, income, goods, and services, globally and nationally, the consequent unfairness in the immediate, visible circumstances of people's lives—their access to health care, schools, and education, their conditions of work and leisure, their homes, communities, towns, or cities—and their chances of leading a flourishing life. (p. 1)

Evidence consistently indicates that inequalities in health follow a social gradient—that is, globally, the "poorest of the poor" tend to have the worst health outcomes—and even within the highest income countries, poorer health outcomes are disproportionately experienced by individuals in lower socioeconomic positions [126-128]. While the ultimate goal of health equity is to see improvement in health outcomes across an entire population, specific emphasis is placed on minimizing inequalities in access to health services and poor health outcomes among key, "vulnerable" populations who are both socially and economically disadvantaged [128, 129]. As such, there is a general acknowledgement in the literature that in order to achieve healthy equity, work must be done to untangle the complex relationship between the social determinants of

health—including structural drivers, such as social and economic policies, and the conditions of daily life—and inequalities in health outcomes, as well as inequalities in access to, and utilization of health services [127, 130-132].

In 2015, building upon the Millennium Development Goals (MDGs), the Sustainable Development Goals (SDGs) were introduced to the world by the United Nations in an unprecedented commitment to "achieving sustainable development in its three dimensions—economic [development], social [inclusion] and environmental [sustainability]—in a balanced and integrated manner" [133, p. 4]. Whereas three of the eight MDGs were specifically focused on health (MDG 4: reduce child mortality, MDG 5: improve maternal health, and MDG 6: combating HIV/AIDS, malaria, and other diseases) [134], just one of the seventeen SDGs is explicitly health-focused (SDG 3: Ensure healthy lives and promote well-being for all at all ages) [133], albeit with nine specific targets spanning issues such as maternal, neonatal, and child health; tuberculosis, malaria, and other neglected and tropical infectious diseases; problematic substance use; and sexual and reproductive health, including STBBIs and HIV [135]. However, what the SDGs have that the MDGs lacked, is a central message that focuses on equity, and specifically, "combat[ing] inequalities within and among countries" [133, p. 4]. Indeed, Marmot and Bell [132] suggest that, "health equity provides a cross-cutting theme, within an evidence-based conceptual framework, that would help countries develop coherent action across the sectoral goals and target areas of the SGDs" (p. 6), highlighting the overlap between the implicit focus on the social determinants of health across the seventeen SDGs and the explicit call to action upon the social determinants of health in order to achieve health equity through the reduction of inequalities in health outcomes, access to, and utilization of health services [132, 136].

2.1.1.1 Inequalities in access and utilization of health services: The Tanahashi model of health service coverage

In 1978, Tanahashi [137] proposed a model of health service coverage, which outlines five sequential dimensions of coverage that are fundamental to the successful provision of health services to a given target population—typically a subgroup of the total population (see Figure B.1 in Appendix B). First, *availability coverage* refers to the maximum capacity of a service, based upon the resource availability, in relation to the target population size, and is useful for understanding the potential reach of the service. Next, *accessibility coverage* is a measure of the actual reach of the service and is useful for understanding the number of people who are able to use an available service. Accessibility coverage may be limited, for example, by the geographic location in which a service is being provided. The third dimension is *acceptability coverage*, which refers to the proportion of people within the target population who are willing to use the service that is accessible to them. Acceptability of a service is likely to vary at the individual-level, but may be impacted by factors such as service cost, users' belief system, or wait time [137, 138]. *Contact coverage* is the fourth dimension of coverage and refers to the actual contact between a service user and the provider; it measures the utilization of the service within the proportion of the target population who found the service to be acceptable. Finally, *effectiveness coverage* considers the number of people who receive "satisfactory" or effective service among those who use it. While these five dimensions of coverage are described in relation to service provision, they can be further characterized by whether they are supply- or demand-side determinants of service provision [137, 138]. Specifically, the first two dimensions, availability and accessibility coverage, are supply-side determinants as they pertain to aspects of coverage that are controlled by a health system (that is, resource availability and allocation and service design and delivery), while acceptability coverage, contact coverage, and effectiveness coverage

are predominantly determined by demand-side factors at the individual- or community-levels [138] and are measured based upon assessments by service users.

The Tanahashi model [137] is directly relevant to the concept of health equity in that it provides a framework with which to conceptualize and identify inequalities in access to and utilization of health services at a population-level. The concept of *population-specific coverage*, articulated by Tanahashi [137], describes the disaggregation of the five dimensions of coverage by subgroups of the target population, defined by factors unrelated to service provision. The author notes that population-specific coverage is "useful in the analysis of interactions between service provision and factors affecting the target populations" [137, p. 298], such as, for example, demographic and socioeconomic characteristics.

2.1.1.2 Measuring health inequalities: A necessary step toward health equity and achieving the Sustainable Development Goals

With all of this in mind, there is a clear, global imperative to ensure that health research prioritizes issues of inequity, specifically in relation to inequalities in health outcomes and access and utilization of health services that are both unjust and unavoidable. Effectively monitoring health inequalities at global, national, and sub-national levels requires strong health data infrastructure [139] that facilitates disaggregated analyses of health data [131, 132, 137, 139] so that governments, health systems, and health programs are able to *recognize* inequalities within and between groups. Furthermore, it is crucial that global policy normative bodies provide technical and logistical support to countries working toward these goals [127, 132, 139].

However, the use of quantitative data for the identification of inequalities is not sufficient evidence upon which to develop programs or policies that are meant to work toward achieving health equity. Indeed, as far back as 1978, Tanahashi [137] recognized that a "good knowledge

of the health service and of the situation of the target population is… required in order to analyse the constraining factors" (p. 300) responsible for inequalities in health service coverage. Thorough understandings of *why* inequalities exist, and *how* they are sustained and upheld are also necessary to adequately inform effective policy and programming [137, 139-141], and are best achieved through a combination of qualitative and quantitative approaches, with the meaningful involvement of key affected populations [139, 141]. However, even once appropriate systems are in place to collect these necessary contextualizing data, an effective strategy for integrating this evidence into programs and policies is required.

2.1.2 Program Science: A strategy for generating and incorporating knowledge for service optimization

In 2011, Blanchard and Aral [142] introduced the concept of Program Science as an approach to improving the design and implementation of public health programs through the systematic application of theoretical and empirical scientific knowledge. At its core, Program Science is a framework for both program implementation and research, defined by an iterative process whereby empirical and situated knowledge derived from programs drives scientific inquiry, which then produces further evidence that is incorporated into programming for service optimization [143]. Within the Program Science framework, a public health program is conceptualized as a complex system with emergent properties that comprises multiple components (interventions) tailored to a specific context, with the ultimate goal of maximizing population-level impact of a program by optimizing "the choice of the right strategy for the right populations at the appropriate time; by doing the right things the right way; and by ensuring appropriate scale and efficiency" [142, p. 2]. In this way, Program Science inherently embraces an equity focus as it is concerned with prioritizing target populations who will benefit most from

program activities and services, and allocating resources such that program activities are accommodating the needs of "key" populations [142-144]. As an approach, Program Science can be differentiated from other similar frameworks, such a Implementation Science [145] and Translational Science [146], by: (i) its focus on the effective implementation of the entirety of a program rather than a single intervention [143, 147]; (ii) the embeddedness of the research process within each of a program's components parts [144]; and (iii) the bidirectional approach of extracting knowledge from programs through embedded scientific inquiry, formulating new hypotheses and questions, and then incorporating new research back into programs [142, 143, 148]. Programs that are implemented using a Program Science framework are continuously and systematically monitoring program activities—including indicators, outcomes, and outputs of interest—and thoroughly documenting implementation processes throughout a program's lifespan [149]. Through this enhanced monitoring and evaluation process—which, ideally, involves mixed-methodologies [149]—research questions and context-specific, situated knowledge emerge that can inform the optimization of program activities, with respect to service delivery and uptake, and provide a basis upon which implementers can make decisions about how to adjust their programs to accommodate the evolving needs of those accessing services.

2.1.3 Operationalizing the principles of health equity and Program Science to address inequalities across the HIV care cascade in Manitoba

Becker and colleagues [143] highlight a number of instances in which the principles of Program Science have been successfully applied to programs, research, and policy development focused on HIV and STI prevention, globally. Less commonly have Program Science principles been applied to programs, research, and policy focused on HIV care. This dissertation comprises work that highlights how data from disparate sources, including the Manitoba HIV Program and

MHSAL administrative health datasets, can be: (i) brought together to form a cohesive dataset in the form of a clinical cohort; (ii) used to develop a framework—in this case, a locally relevant HIV care cascade model—that can monitor and evaluate program indicators and outputs, including service coverage and health outcomes; then (iii) systematically and critically analyzed through the framework to identify bottlenecks in service coverage at aggregate- and disaggregate levels.

While a handful of studies have examined inequalities in HIV care outcomes among different sociodemographic groups [100, 150-157], the work presented in this dissertation is among the first to conduct a comprehensive, quantitative equity analysis examining the association of various sociodemographic variables with each step across the entire HIV care cascade. Notably, a recent systematic review focusing on sociodemographic heterogeneity across the cascade in sub-Saharan African counties [151], identified 92 studies that examined at least one cascade step or 90-90-90 target, but very few examined inequalities across the entire care cascade, and most focused only on age, sex, and/or ethnicity. Using an "equity lens" to examine complexities within a conventional, aggregate HIV care cascade model is a novel, though relatively simple strategy, that greatly enhances the programmatic utility of cascade data. This approach demonstrates how the HIV care cascade can be used as a tool that forces health systems and public health programs to explicitly confront issues in the delivery and uptake of HIV care that arise from the different needs and experiences of subgroups of people living with HIV.

Ultimately, following Program Science principles, the knowledge and evidence generated (largely from program-derived data) through the presented studies can be conceptualized as key components of a larger toolbox of essential data and strategies that can be effectively incorporated back into "practice"—including Manitoba HIV Program activities and relevant

provincial policies—as we collectively work toward a more equitable system of healthcare in Manitoba.

2.2 Research objectives and dissertation overview

The work compiled in this dissertation aims to contribute to a more comprehensive understanding of Manitoba's HIV epidemic through the development of a provincial HIV care cascade and a subsequent critical exploration of the variation and inequalities across the cascade. Specifically, it brings together a series of studies that aim to generate evidence, knowledge, and specific tools that can be used to further our understanding of the most effective ways to optimize coverage of HIV care in Manitoba and work towards achieving equity in the health and well-being of people living with HIV in the province.

The specific research objectives of this dissertation are three-fold:

Objective 1. To develop a clinical cohort of people living with HIV in Manitoba.

Objective 2. To develop an HIV care cascade model, including locally relevant indicator definitions based on clinical cohort data, for Manitoba.

Objective 2a. To derive estimates for each step of the Manitoban HIV care cascade.

Objective 3. To examine the HIV care cascade through an equity lens and identify inequalities in care provision and utilization among people living with HIV in Manitoba.

The first objective of this work is addressed in Chapter 3, which focuses on the development of the LHIV-Manitoba clinical cohort (hereafter, alternatively referred to as "the

clinical cohort" or "the cohort"). This work describes the first ever prospective cohort of people living with HIV in Manitoba and provides an in-depth description of the cohort development process; the clinical and provincial, administrative health datasets included within the cohort; and highlights select key findings based upon preliminary analyses of the clinical data. Importantly, Chapter 3 sets the stage for work presented in subsequent chapters—all of which is based upon clinical cohort dataset. Next, addressing objectives 2 and 2a, Chapter 4 details the steps taken to develop HIV care cascade indicator definitions tailored to the Manitoban context, and presents the first HIV comprehensive care cascade for Manitoba using data from clinical cohort described in Chapter 3. This study also examines numerous alternative indicator definitions for each cascade steps that could be used to generate cascade estimates in a context where data availability or other resources are limited. Finally, building upon the work in Chapter 4 while addressing the third research objective, Chapter 5 dives deeper into the Manitoban care cascade to examine the data through an "equity lens". Here, multiple versions of the care cascade are generated by disaggregating data by variables of interest and illustrated as equiplots, as a way to examine how HIV care and relevant health outcomes differ for various subgroups within the clinical cohort population.

Knowledge gathered throughout this work is intended to contribute to the development of improved programming strategies within the Manitoba HIV Program that address bottlenecks and inequalities in the delivery and uptake of services and in health outcomes. Furthermore, the evidence presented in these studies, taken together with additional research using complementary methodologies, has the potential to inform provincial policies related to the provision of HIV care, that would support the effective and timely navigation through Manitoba's health system for people living with HIV.

2.3 Ethical considerations

2.3.1 Ethics approvals

Ethics approval for this dissertation was obtained from the University of Manitoba's Health Research Ethics Board (UM-HREB, HS21678). The larger LHIV study, in which this work is embedded, received approvals from UM-HREB (HS15817); the Health Sciences Centre's Research Impact Committee; the Health Information Privacy Committee (HIPC) of MHSAL (HIPC#2015/16-63); and the Nine Circles Community Health Centre Research Committee. The cohort study has also received support from the Health Information Research Governance Committee of *Nanaandawewigamig*, the First Nations Health and Social Secretariat of Manitoba.

2.3.2 Informed consent procedures

All individuals whose data are included in this dissertation provided informed consent to participate in the LHIV-Manitoba clinical cohort (see Table B.1 and Table B.2 in Appendix B). Specifically, the consent process involved a multistep process in which potential participants had the opportunity to take part in any combination of three separate components of the clinical cohort study: (i) have their clinical data collected; and/or (ii) have their de-identified clinical data anonymously linked to administrative health data that is routinely collected by the province; and/or (iii) indicate interest in being approached about future HIV research studies. Participant recruitment into the cohorts and informed consent took place within the context of clinical appointments within the Manitoba HIV Program. Unique, alphanumeric study codes replaced all personal information that could potentially identify a participant, including names, address, and personal health identification number (PHIN). A more detailed description of specific recruitment and informed consent procedures is outlined in Chapter 3.

2.3.3 Engagement with stakeholders

Throughout the work presented in this dissertation, the local study team and I actively partnered with stakeholders within the Manitoba HIV Program and other community clinics, MHSAL, the Manitoba First Nations AIDS Working Group, and the LHIV study's Community Scholar Program [158], and provided opportunities for active involvement in the development of the clinical cohort. Over the course of this work, engagement through community forums and meetings with key stakeholders, particularly the Manitoba HIV Program Leadership Team, informed the development of the objectives of this dissertation. As such, cumulative findings from these studies are expected to have direct relevance and applicability for both HIV care programming and provincial health policy. Following suit, dissemination and future knowledge translation activities will actively involve key stakeholders, including community members, community-based organizations, and policy- and decision-makers.

Preface to Chapter 3

Chapter 3 is adapted from a manuscript published in *BMJ Open*. This work describes the processes involved in the development of a clinical cohort that was established under the umbrella of the larger LHIV study. It details the cohort participant enrolment procedures, describes the datasets contained within the cohort, presents a profile of the cohort participants' sociodemographic characteristics, and summarizes key findings from preliminary analyses of cohort data. The contents of this chapter lay the foundation for subsequent chapters, which use the clinical cohort as a primary source of data to explore and critically analyze patterns and trends in HIV care in Manitoba.

Contribution of authors

I played a significant role in the conceptualization and design of the LHIV-Manitoba cohort study, along with Drs. Eve Cheuk, Claire Kendall (the nominated principle investigator of the LHIV study; CIHR funding reference number TT5-128270), and Marissa Becker (co-investigator and lead for the Manitoba site of the LHIV study). I was responsible for data collection and procurement for this work, and received help reviewing clinic files along the way from Dr. Christopher Briggs, Dr. Adam Erickson, Dr. Elsabé du Plessis, Nicole Herpai and Michael Paillé, with oversight throughout from Drs. Laurie Ireland, Ken Kasper, Yoav Keynan, and Marissa Becker. Nicole Herpai helped with participant recruitment and Dr. Marissa Becker, Dr. Souradet Shaw and Stella Leung supported administrative data procurement. I was solely responsible for writing this paper and conducting all analyses contained within it. I received feedback and/or critical revisions on the manuscript from all listed co-authors.

Citation details

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Chapter 3. Cohort Profile: The LHIV-Manitoba Clinical Cohort of People Living with HIV in Manitoba, Canada

Abstract

The LHIV-Manitoba cohort was developed as a way to provide a comprehensive source of HIV-related health information in the central Canadian Prairie province of Manitoba. The cohort will provide important information as we aim to better understand local HIV epidemiology and address key knowledge and practice gaps in HIV prevention, treatment, and care programming in the province.

In total, 890 individuals, aged 18 or older and living or receiving HIV care in Manitoba are enrolled in the cohort. A complete clinical dataset exists for 725 participants, which includes variables on socio-demographic characteristics, comorbidities and co-infections, self-reported HIV exposure categories, and HIV clinical indicators. A limited clinical dataset exists for an additional 165 individuals who were enrolled posthumously. 97.5% of cohort participants' clinical records are linked to provincial administrative health datasets.

The average age of cohort participants is 49.7 years. Approximately three-quarters of participants are male, 42% self-identified as white and 42% as Indigenous. The majority of participants (64%) reported condomless vaginal sex as a risk exposure for HIV. Nearly one-fifth (18%) of participants have an active HCV infection and the cohort's median CD4 count increased from 316 to 518 cells/mm^3 between time of entry into care to end of the first quarter in 2019.

The LHIV-Manitoba cohort is an open cohort, and as such, participant enrolment, data collection, and analyses will be continually ongoing. Future analyses will focus on the impact of provincial drug plans on clinical outcomes, determinants of mortality among cohort participants, and deriving estimates for a local HIV care cascade.

3.1 Introduction

Annual reports on HIV in Canada consistently highlight heterogeneous, albeit relatively stable, epidemiological trends across the country [22]. At the end of 2018, PHAC estimated that 88,881 people were living with HIV in the country and 2,561 people were newly diagnosed in the same year [17]. Nationally, new HIV diagnoses disproportionately occur among Indigenous (First Nations, Inuit, and Métis) populations and people who have immigrated from countries where HIV is endemic [22]. The greatest proportion of prevalent HIV infections in nearly all Canadian provinces are attributed to condomless sex between men; however, notable exceptions include the central Prairie provinces of Saskatchewan and Manitoba, where most incident and prevalent cases are attributable to injection drug use and heterosexual transmission, respectively [21, 159, 160]. Rates of new HIV diagnoses per 100,000 population in Manitoba have been consistently higher than the national average, ranging from 9.5 new diagnoses in 2014 to 6.6 in 2016 and 2017 [20-22], and 7.9 in 2018 [17]. Despite evidence of unique epidemiology and disproportionately high rates of infection, relatively little research addresses HIV epidemiology in the Canadian Prairies [28], and there is a specific lack of published research focusing on Manitoba.

Current HIV epidemiological data for Manitoba are primarily derived from surveillance reports produced by PHAC and the provincial health department, MSHAL [22, 159]. In 2018, MHSAL reported 107 new cases of HIV in the province with the majority of cases occurring in Winnipeg (78%) and a disproportionately high incidence among women when compared to national rates [24]. While useful for providing basic information about patterns and trends in HIV infection in Manitoba, these reports only provide aggregate-level demographic- and geographic analyses of the previous year's incident infections (new diagnoses and/or cases

introduced to, but not acquired in, the province). Without clinical data, these reports are limited in their ability to inform specific research questions or programmatic decisions for HIV care and service delivery in the province.

In 2013, as part of a Canadian Institutes of Health Research-funded program of research, the "Advancing Primary Health Care for Persons Living with HIV in Canada" (LHIV) study provided support for the establishment of a prospective clinical cohort of people living with HIV in Manitoba. This clinical cohort is the first comprehensive source of HIV-specific health data in Manitoba and provides important opportunities to address key knowledge gaps in local HIV epidemiology—including patterns of healthcare utilization and relevant clinical outcomes—and to understand healthcare needs of people living with HIV in the province. Similar cohorts have been developed and are now are well-established in other Canadian provinces, including British Columbia [34] and Ontario [35]. This article provides an overview of processes and procedures involved in cohort development and maintenance and describes demographic- and HIV-related characteristics of LHIV-Manitoba cohort participants.

3.2 Methods

3.2.1 Study setting

Established in 2007, the Manitoba HIV Program is the primary provider of treatment, care, and support for people living with HIV in the province. The Manitoba HIV Program employs a multidisciplinary care model in which HIV specialist physicians, family physicians, nurses (including nurse practitioners), pharmacists, dieticians, social workers, and other allied service providers provide comprehensive HIV care out of three clinic sites—a hospital-based outpatient clinic and a community health centre in Manitoba's capital city, Winnipeg, and a nurse-run health access centre in Brandon, a semi-urban city approximately 200 kilometres west

of Winnipeg (Figure 3.1). While all three clinic sites follow a multidisciplinary care model and each have links to health promotion programs and community resources, some differences in organization exist. For example, the clinic at the community health centre is located in the downtown neighbourhood of Winnipeg and provides comprehensive primary care to individuals living in their catchment area. Specializing in STBBI-specific services for people living with or without HIV, the community health centre is run by family doctors and each client at that site is assigned to a specific physician and nurse couple. Meanwhile, physicians at the hospital-based clinic, also located in downtown Winnipeg, are Infectious Disease specialists. During appointments, clients at the hospital-based clinic are seen by a rotating roster of physicians and nurses, in addition to other providers, as needed. The nurse-run clinic in Brandon operates in a similar manner, in which clients are seen by a rotating roster of providers, allied health professionals, and community support workers.

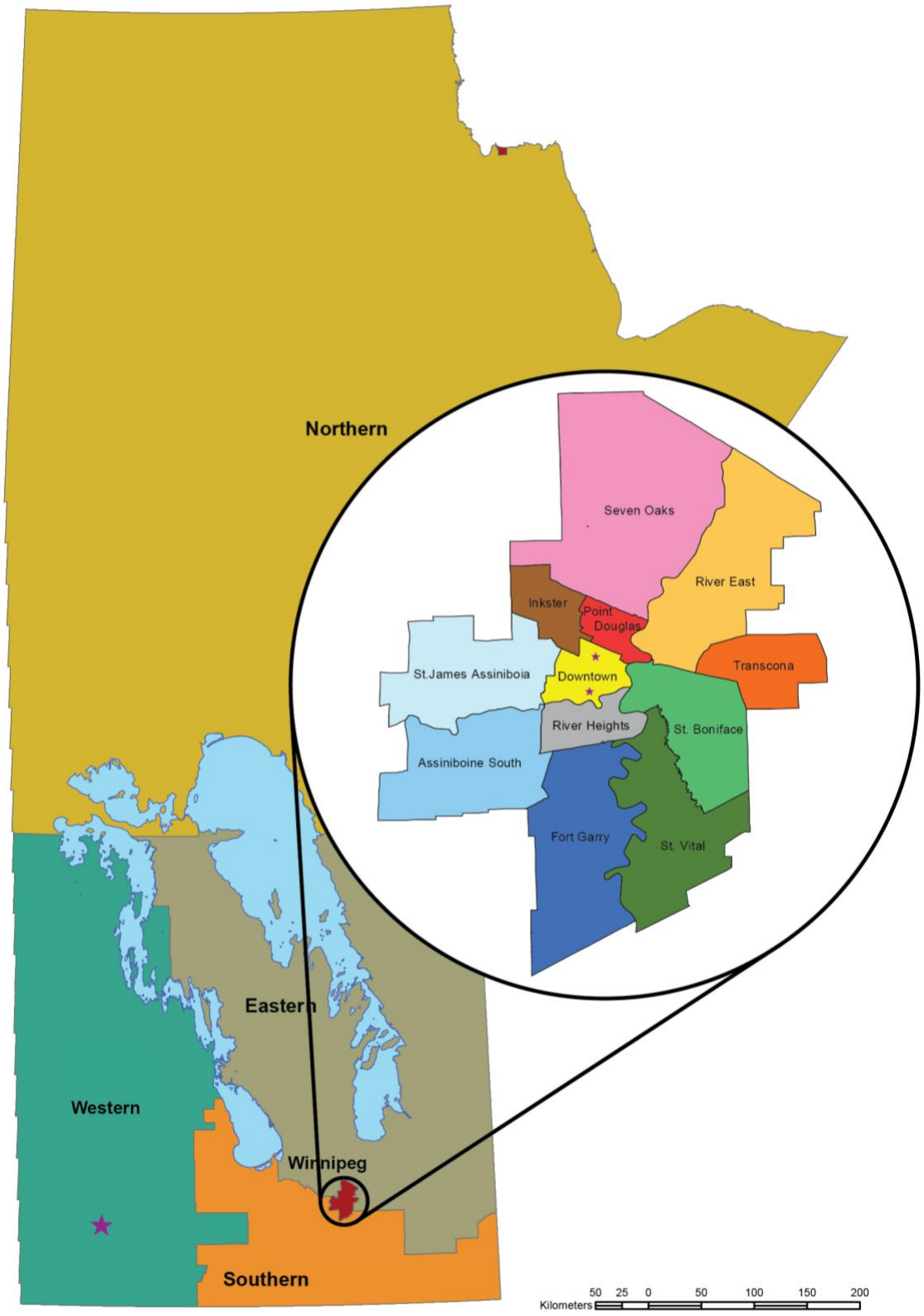

Figure 3.1. Geographic distribution of Manitoba HIV Program clinic sites (purple stars). Figures adapted from MHSAL and the Winnipeg Regional Health Authority.

3.2.2 Patient and public involvement

Although arising from a research project, the LHIV-Manitoba cohort is strategically embedded within the Manitoba HIV Program and the local study team partners with stakeholders within the Manitoba HIV Program and other community clinics, MHSAL, the Manitoba First Nations AIDS Working Group, and the LHIV study's Community Scholar Program [158], all of whom have been actively involved in the development of the cohort. Study design and enrolment procedures were conducted by researchers and trainees within the LHIV study team. Throughout the development of the cohort, engagement through community forums and meetings with key stakeholders provided information about the objectives of the LHIV-Manitoba cohort and what it meant to be a participant, while actively seeking input about research questions that could be addressed using cohort data. As such, findings from cohort data are expected to have direct relevance and applicability for both HIV care programming and provincial health policy. Dissemination and knowledge translation activities with all key stakeholders, including community members, community-based organizations, and key policy- and decision-makers, will be facilitated by study team members and Manitoba HIV Program staff.

3.2.3 Enrolment procedures

Recruitment efforts to identify cohort participants began at one clinic site in October 2013 and was fully implemented across all Manitoba HIV Program sites by January 2014. Clinical data collection, data cleaning and analyses began in early 2017, and will be continuous processes as long as enrolment proceeds.

As the LHIV-Manitoba clinical cohort is an open cohort, enrolment is ongoing. The enrolment process is illustrated in Figure 3.2. Inclusion criteria for the cohort are broad: participants must be at least 18 years of age and either living with HIV in Manitoba or receiving

HIV care in Manitoba. Individuals who met these criteria but are under the jurisdiction of the Public Guardian and Trustee of Manitoba or were otherwise unable to make decisions pertaining to their own healthcare, are deemed ineligible for participation in the cohort.

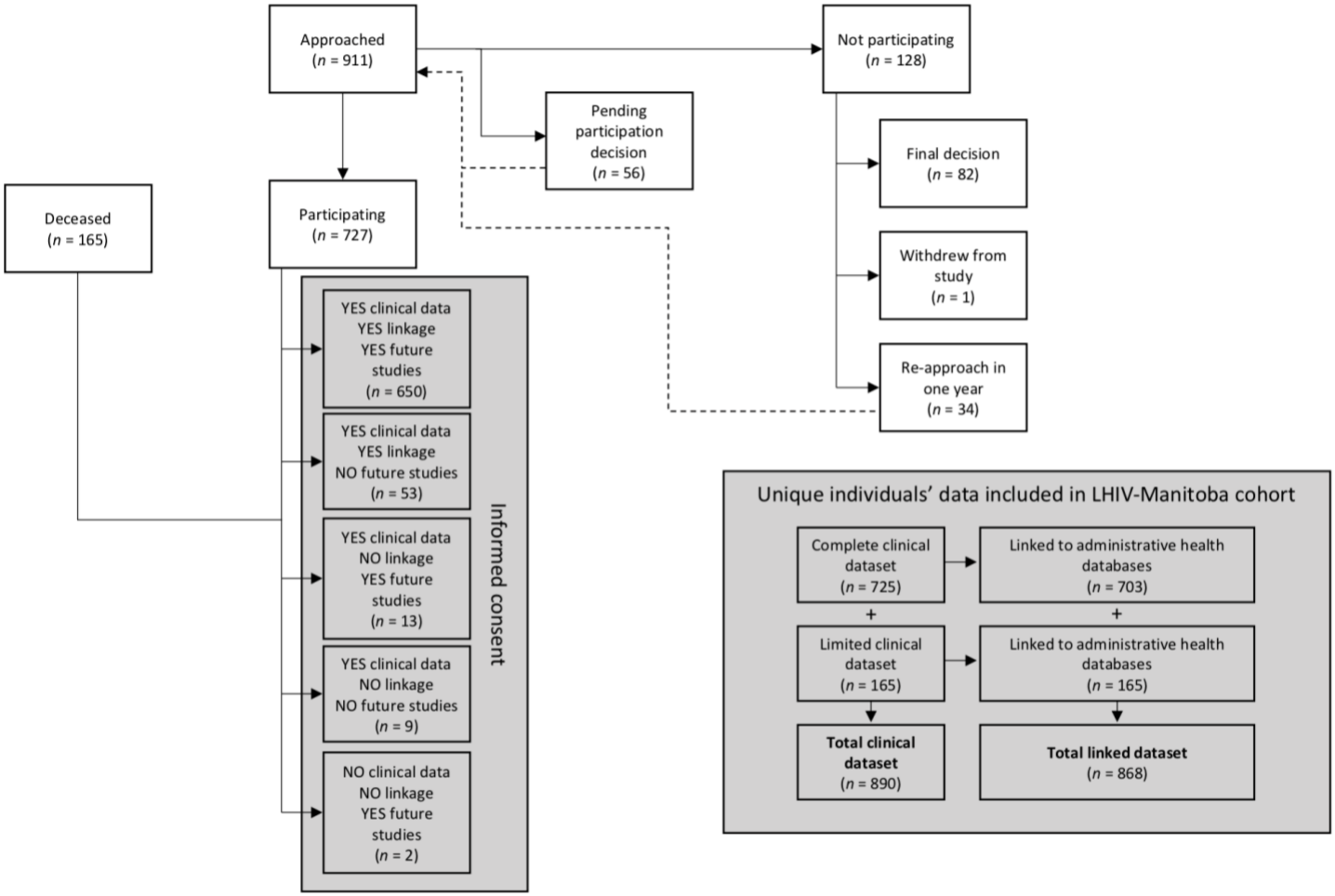

Figure 3.2. Recruitment, informed consent, and data collection processes for the LHIV-Manitoba clinical cohort.

Recruitment and informed consent procedures take place within the Manitoba HIV Program clinics; clients who present to clinic are approached by a nurse or another allied healthcare provider and asked whether they are willing to speak to a research assistant about participating in a research project. If a client is agreeable, a research assistant meets with them to explain the purpose, context, and methods for the LHIV-Manitoba cohort study, and reviews the informed consent form to determine whether the person is interested, willing, and able to participate. Participants have the opportunity to take part in any combination of three separate components of the LHIV-Manitoba cohort: (i) have their clinical data collected; and/or (ii) have their clinical data linked to administrative health data that is routinely collected by the province; and/or (iii) indicate interest in being approached about future HIV research studies. Clients who are not ready to decide immediately can defer their decision to participate in the cohort and request to meet with the research assistant at a later date to reconsider their participation. Study staff keep track of individuals who asked to defer their decision to participant and actively follow-up with them at their next clinic appointment in a year's time, depending on stated preference.

3.2.4 Study measures, data sources, and data collection

Clinical data are manually extracted from electronic medical records (EMR)—or from paper charts if relevant clinical information was recorded prior to the introduction of EMR to clinic sites—within the Manitoba HIV Program's clinic sites by the first author and two trained extractors, and then entered into an encrypted, password protected Microsoft Excel spreadsheet for consenting participants. Standardized definitions were developed for each variable to ensure quality and consistency of data abstracted from clinical records. The Manitoba HIV Program clinicians who had entered data into clinical records were consulted for instances in which

information to be collected was unclear or ambiguous. A complete clinical dataset for the LHIV-Manitoba cohort includes variables on participants' socio-demographic characteristics (age, sex, geographic location of residence, self-identified ethnicity); comorbid chronic- and mental health diagnoses, opportunistic- and other co-infections (occurring within 6-months of presentation to HIV care), including Hepatitis C virus (HCV); recorded HIV exposure categories; date and geographic location of first positive HIV test; CD4 count at time of diagnosis, at time of ART initiation, and at the end of the second and fourth quarters of each year, beginning in 2017; date of first ART initiation; current ART regimen (collected biannually, beginning in 2017); alcohol and drug use, including injection drug use; and type of prescription pharmaceutical insurance coverage (collected biannually, beginning in 2017). The data dictionary describing all clinical variables included in the cohort is included as Table C. 1 in Appendix C

The study's institutional ethics approvals also allow data from deceased clients of the Manitoba HIV Program to be collected via retrospective chart reviews. A limited dataset is extracted from clinical records of deceased individuals, which comprises a subset of the aforementioned clinical datasets, excluding all comorbidity and co-infection data from clinical records, except for HCV; treatment regimen data; and prescription pharmaceutical insurance data. Including data from deceased clients provides an important opportunity to explore and better understand determinants of mortality among people living with HIV in Manitoba. This has been identified as an area of particular interest to the Manitoba HIV Program, which, up to now, has not been adequately explored. Furthermore, the inclusion of these data helps to ensure broader generalizability of our findings from the cohort.

For individuals who were enrolled posthumously, and for participants who provide consent to data linkage, anonymized, de-identified clinical data are linked to provincial

administrative health databases housed at MHSAL. Manitoba's administrative health datasets include individual-level records for nearly all contacts with the provincial healthcare system, including physician visits, hospital admissions, pharmaceutical prescription dispensations, and laboratory testing [161]. Linkage between clinical and administrative datasets is done through matching an individual's unique Personal Health Identification Number (PHIN) within both datasets. Before linked datasets are returned to the study team, MHSAL scrambles PHINs to de-identify the datasets and maintain participant anonymity [162]. Table C. 2 in Appendix Coutlines all provincial administrative health datasets, and variables within them, included in the LHIV-Manitoba cohort database. At the time of writing, linkage of clinical data to provincial administrative health databases is current up to the end of 2017. Updated clinical data will be re-linked to updated administrative datasets on an approximately biennial basis, or as needed. Linked clinical cohort data are securely stored within the Public Health Data Laboratory (PHDL) at the Institute for Global Public Health, University of Manitoba. The PHDL can be accessed by swipe card only and the network in which datasets are stored is protected by an electronic firewall and a virtual private network (VPN) with a double-password login system.

Missing data are minimal throughout the clinical cohort data set and are excluded from analyses. Of the 890 unique individuals included in the cohort, only 9.1% (n = 81) of participants were missing observations from at least one key variable of interest—CD4 counts and viral loads (Table C. 3 in Appendix C). Some variations in missingness were observed across participants' age, sex, ethnicity, or geography (see Table C. 4 through Table C. 7 in Appendix C). Notably, participants for whom region of residence is unknown or not available (that is, do not have permanent postal codes recorded in their clinical files) are disproportionately missing CD4 count and viral load data, warranting cautious interpretation of findings stratified by geography.

3.3 Ethics approvals

The LHIV-Manitoba cohort study received ethics approval from the University of Manitoba's Health Research Ethics Board, the local hospital's Research Impact Committee, and HIPC of MHSAL. This work has also received support from the Health Information Research Governance Committee of *Nanaandawewigamig*, the First Nations Health and Social Secretariat of Manitoba.

3.4 Results

3.4.1 Characteristics of study participants

As of March 31st, 2019, 890 unique individuals are included in the cohort (Figure 3.2). A complete clinical dataset exists for 725 (81.5%) cohort participants who agreed to have their data reviewed and extracted from clinical records within the Manitoba HIV Program. A limited clinical dataset exists for an additional 165 individuals whose clinical records were reviewed posthumously. Nearly all individual-level clinical data are also linked to provincial administrative health datasets (n = 868, 97.5%). At the end of the first quarter of 2019, 676 cohort participants (76.0%) were alive and 214 (24.0%) were deceased.

Select sociodemographic characteristics and outcomes of cohort participants are presented in Table 3.1 and compared to the larger Manitoba HIV Program client population. The average age of cohort participants at the end of the first quarter of 2019 (or at time of death, for participants who were deceased by March 31st, 2019), was 49.7 ± 11.9 years. The majority of cohort participants are male (71.2%), over 80% reported being either white (42.4%) or Indigenous (41.6%), while an additional 10.9% self-identified as an ethnicity categorized as sub-Saharan African/Caribbean/Black. Geographic distribution of cohort participants is primarily concentrated in Winnipeg (80.8%), while 1.4% of cohort participants live outside of Manitoba.

Table 3.1. Sociodemographic characteristics and key outcomes of LHIV-Manitoba cohort participants, as compared to Manitoba HIV Program client population.

	LHIV-Manitoba cohort (*N*=890)		**Manitoba HIV Program (*N*=1,357)**		***p*-value**
	n	%	*n*	%	
Age (years) on March 31, 2019 or at time of death					
<18	0	0	2	0.2	0.245
18-24	10	1.1	46	3.4	0.001
25-39	178	20.0	358	26.4	0.001
40-64	621	69.8	871	64.2	0.006
≥65	81	9.1	78	5.8	0.003
Mean (SD)	49.7 (11.9)		46.8 (12.1)		0.000
Median (IQR)	49.8 (41.5-57.5)		46.9 (37.9-55.2)		0.000
Sex					
Male	634	71.2	878	64.7	0.001
Female	256	28.8	478	35.2	0.002
Self-identified ethnicity*					
White	376	42.4	407	36.2	0.000
Indigenous (First Nations, Inuit, Métis)	369	41.6	448	39.9	0.000
Sub-Saharan African/Caribbean/Black	97	10.9	214	19.1	0.001
Other†	44	5.0	54	4.8	0.307
Region of residence					
Winnipeg	719	80.8	1,080	79.6	0.486
Eastern Manitoba	48	5.4	71	5.2	0.836
Southern Manitoba	37	4.2	67	4.9	0.440

	LHIV-Manitoba cohort (*N*=890)		Manitoba HIV Program (*N*=1,357)		*p*-value
	n	%	*n*	%	
Western Manitoba	35	3.9	64	4.7	0.365
Northern Manitoba	30	3.4	46	3.4	1.000
Out of province	12	1.4	21	1.6	0.705
Unknown/No known address	9	1.0	8	0.6	0.285
Drug coverage at March 31st, 2019‡¶					
Out-of-pocket expenses associated with drug plan	293	45.4	-	-	
No out-of-pocket expenses associated with drug plan	346	53.6	-	-	-
Not on treatment/Unknown	6	0.9	-	-	
Problematic substance use recorded in clinic file§					
Alcohol	292	40.3	-	-	
Illegal or "street" drugs|	222	31.6	-	-	-
Alcohol *and* drugs	148	21.1	-	-	
Has a primary care practitioner§	627	70.5	-	-	-

* Sample sizes may not add up to total participants due to missing data for some variables.
† Includes Latin American, East/Southeast Asian, South Asian, West Asian/North African/Middle Eastern.
‡ Variable only collected for participants alive in the fourth quarter of 2018 (*n*=645).
§ Variable only collected for participants alive at cohort enrolment (*n*=725).
| Includes cocaine, crack cocaine, heroin, crystal methamphetamine, other hallucinogens (Lysergic acid diethylamide [LSD, "acid"], γ-Hydroxybutyric acid [GHB], ketamine, 3,4-Methylenedioxymethamphetamine [MDMA, "ecstasy"]), solvents, Talwin & Ritalin, and alkyl nitrates ("poppers").
¶ Table C. 8 in Appendix Cdescribes which drug plans do or do not involve out-of-pocket expenses.

3.4.2 Key findings to date

Analyses from the LHIV-Manitoba cohort are ongoing; a summary of preliminary findings of interest is provided below.

3.4.2.1 Representativeness and distribution of key outcomes within the LHIV-Manitoba cohort

Given the research and programmatic potential of this cohort, it is of particular interest to understand whether, and to what extent, the demographic profile of cohort participants is representative of the larger Manitoba HIV Program client population (Table 3.1). Although similar in age structure, compared to the Manitoba HIV Program's client population, cohort participants are significantly more likely to be ≥40 years (78.9% vs. 70.0%, p <0.05). Compared to the Manitoba HIV Program, the cohort includes significantly more men (71.2% vs. 64.7%; p = 0.001) and individuals who self-identify as white (42.3% vs. 30.0%, p <0.001) or Indigenous (41.5% vs. 33.0%, p <0.001) are greater in the LHIV-Manitoba cohort, while African/Caribbean/Black clients are underrepresented (10.9% vs. 15.8%, p <0.001). The geographic distribution of cohort participants is similar to that of the larger client population, with the large majority of participants residing in Winnipeg (80.8% vs. 79.6%, p = 0.486).

3.4.2.2 HIV-specific clinical indicators, co-infections, and comorbidities

Select clinical indicators, analysed by sex, are presented in Table 3.2. Preliminary findings from cohort participants' clinical data highlight similar trends to those seen in the most recent Manitoba HIV Program annual reports [26, 27]. While a substantial proportion of cohort participants presented late to HIV care, with 57.0% having initial CD4 counts ≤350 cells/mm3, 52.3% of most recent CD4 counts are >500cells/mm3. In general, the proportion of participants with suppressed viral loads (<200 HIV RNA copies/mL) increased from their initial to most

recent clinic visit (50.5% to 83.2%, respectively). Female cohort participants were significantly more likely than male participants to have unsuppressed viral loads (that is, >200 copies/mL) at presentation to care, but this same difference was not seen when analysing most recent viral load results. Opportunistic infections (OIs) were diagnosed at or within 6-months of presentation to HIV care among 29.1% of participants who were alive at enrolment, and 6.6% presented to care with ≥2 OIs. Prevalence of active HCV co-infection at enrolment is 17.5% among all participants, and slightly higher among female than male participants (19.9% vs. 16.6%). Two-fifths of participants had at least one comorbidity recorded in their clinical records, and 12.8% (*n* = 93) were living with at least two. Compared to the general population of Manitoba in 2017-18, a greater proportion of cohort participants were living with type II diabetes (DM2, 9.3% versus 14.5%, respectively) and chronic obstructive pulmonary disease (COPD, 12.6% versus 17.8%, respectively), while a smaller proportion were diagnosed with hypertension (HTN, 29.2% versus 15.5%, respectively) [163].

Table 3.2. HIV-specific and other clinical indicators among LHIV-Manitoba cohort participants, by sex.

	Male* (*N*=634)		Female* (*N*=256)		Total* (*N*=890)		*p*-value
	n	**%**	***n***	**%**	***n***	**%**	
Initial CD4 count in Manitoba (cells/mm3)							
<200	211	33.8	72	28.7	283	32.3	0.467
200-350	151	24.2	65	25.9	216	24.7	
351-500	117	18.8	47	18.7	164	18.7	
>500	145	23.2	67	26.7	212	24.2	
Mean (SD)	328.2 (248.7)		370.5 (257.1)		340.3 (251.7)		
Median (IQR)	298.5 (116-478.5)		336 (179-517)		316 (129-492)		
Last CD4 count, up to end of 2018 (cells/mm3)							
<200	81	12.8	47	18.6	128	14.5	0.064
200-350	88	14.0	38	15.0	126	14.3	
351-500	130	20.6	38	15.0	168	19.0	
>500	332	52.6	130	51.4	462	52.3	
Mean (SD)	589.3 (303.6)		331.7 (302.0)		542.2 (319.1)		
Median (IQR)	565 (384-768)		256 (99-472)		517.5 (309.5-735.5)		
Initial viral load (HIV RNA copies/mL)							
<200	329	54.7	100	40.3	429	50.5	0.001†
200-999	27	4.5	16	6.5	43	5.1	
1,000 – 99,999	147	24.5	90	36.3	237	27.9	
100,000 – 999,999	80	13.3	36	14.5	116	13.7	

	Male* (*N*=634)		Female* (*N*=256)		Total* (*N*=890)		*p*-value
	n	**%**	***n***	**%**	***n***	**%**	
≥1,000,000	18	3.0	6	2.4	24	2.8	
Mean (SD)	125,778.7 (523,975.9)		107,972 (340,114.2)		120,577.2 (477,511.4)		
Median (IQR)	60.9 (0-38,400)		1,875 (0-40.300)		170 (0-38,800)		
Last viral load, up to end of 2018 (copies/mL)							
<200	491	84.4	190	80.2	681	83.2	
200-999	22	3.8	9	3.8	31	3.8	
1,000 – 99,999	46	7.9	28	11.8	74	9.0	0.517†
100,000 – 999,999	18	3.1	8	3.4	26	3.2	
≥1,000,000	5	0.9	2	0.8	7	0.9	
Mean (SD)	40,972 (415,359.2)		27,705 (171,693.3)		37,133.2 (362,048.3)		
Median (IQR)	0 (0-27.9)		0 (0-54.6)		0 (0-32.4)		
Opportunistic infections (OIs) ‡§							
None	364	69.9	150	73.5	514	70.9	
Oropharyngeal/esophageal candidiasis (thrush)	108	20.7	39	19.1	147	20.3	
Pneumocystis jirovecii pneumonia (PJP)	56	10.8	9	4.4	65	9.0	0.131†
Active tuberculosis	29	5.6	14	6.9	43	5.9	
Mycobacterium avium-intracellulare (MAI)	7	1.3	1	0.5	8	1.1	
Cryptococcal meningitis	4	0.8	1	0.5	5	0.7	
Hepatitis C virus status at cohort enrolment							
No infection	496	78.2	182	71.1	678	76.2	0.085†
Active infection (RNA+)	105	16.6	51	19.9	156	17.5	

	Male* (*N*=634)		Female* (*N*=256)		Total* (*N*=890)		*p*-value
	n	**%**	***n***	**%**	***n***	**%**	
Past infection (RNA-/Ab+)	32	5.1	22	8.6	54	6.1	
Unknown	1	0.2	1	0.4	2	0.2	
Comorbidities‡‖							
None	305	58.5	125	61.3	430	59.3	
Asthma/COPD	93	17.9	36	17.7	129	17.8	
Hypertension (HTN)	88	16.9	24	11.8	112	15.5	0.006†
Type II diabetes (DM2)	66	12.7	39	19.1	105	14.5	
Coronary artery disease (CAD)	33	6.3	3	1.5	36	5.0	

* Sample sizes may not add up to total participants due to missing data for some variables.

† Some expected values <5, so *p*-values must be interpreted with caution.

‡ Variable only collected for participants who were alive at cohort enrolment; Male, *n* = 521; Female, *n* = 204; Total, *n* = 725.

§ Diagnosed at, or within 6-months of presentation to care with the Manitoba HIV Program. Sum of categories exceeds total sample size because some participants presented with ≥1 OI.

‖ Sum of categories exceeds total sample size because some participants presented with ≥1 comorbidity.

3.4.2.3 HIV exposures among cohort participants

Table 3.3 presents all self-reported HIV exposure categories recorded in participants' clinical files, analysed by sex. Although data in Table 3.3 are organized according to an HIV "risk hierarchy"—through which participants' primary risk exposure categories are assigned according to an established hierarchy of risk factors [164]—we report multiple exposure categories per individual in order to capture some of the complexity that can be missed with conventional hierarchy frameworks [165]. Notably, 41.0% of female participants reported at least two possible HIV exposure categories, while 29.6% of men reported the same. Similar to trends from annual surveillance reports in Manitoba [26, 27, 159, 166], condomless vaginal sex is the most commonly identified exposure category. Nearly half of male participants (47.6%) reported condomless anal sex with other men as a possible exposure, and 4.4% reported both condomless anal sex with men and injection drug use. The majority of female participants (92.6%) reported condomless vaginal sex as a possible exposure, and 26.2% reported injection drug use.

Table 3.3. Self-identified HIV exposure categories among LHIV-Manitoba cohort participants, by sex.

	Male* (***N***=634)		**Female*** (***N***=256)		**Total** (***N***=890)		***p*-value**
	n	%	*n*	%	*n*	%	
Condomless anal sex between males + injection drug use	**28**	**4.4**	**-**	**-**	**28**	**3.1**	**-**
Condomless anal sex between males	**302**	**47.6**	**-**	**-**	**302**	**33.9**	**-**
+ *Recipient of blood/blood product*	3	1.0	-	-	3	0.3	
+ *Condomless vaginal sex*	50	16.6	-	-	50	5.6	
+ *Possible exposure in an HIV-endemic country*†	5	1.7	-	-	5	0.6	
+ *Occupational exposure*	2	0.7	-	-	2	0.2	
Injection drug use	**126**	**19.9**	**67**	**26.2**	**193**	**21.7**	**0.039**
+ *Recipient of blood/blood product*	5	4.0	2	3.0	7	0.8	
+ *Condomless vaginal sex*	80	63.5	56	83.6	136	15..3	
+ *Possible exposure in an HIV-endemic country*†	1	0.8	0	0	1	0.1	
+ *Occupational exposure*	1	0.8	1	1.5	2	0.2	
Recipient of blood/blood product	**18**	**2.0**	**8**	**0.9**	**26**	**2.9**	**0.248**
+ *Condomless vaginal sex*	11	61.1	6	75.0	17	1.9	
+ *Possible exposure in an HIV-endemic country*†	2	11.1	1	12.5	3	0.3	
+ *Occupational exposure*	1	5.6	2	25.0	3	0.3	
Condomless vaginal sex	**331**	**52.2**	**237**	**92.5**	**568**	**63.8**	**<0.001**
+ *Possible exposure in an HIV-endemic country*†	35	10.6	40	15.6	75	8.4	
+ *Occupational exposure*	2	0.6	4	1.7	6	0.7	
Occupational exposure	**5**	**0.8**	**4**	**1.6**	**9**	**1.0**	**0.285**
+ *Possible exposure in an HIV-endemic country*	0	0	0	0	0	0	

	Male* (*N*=634)		Female* (*N*=256)		Total (*N*=890)		*p*-value
	n	%	*n*	%	*n*	%	
Possible perinatal acquisition	**1**	**0.2**	**0**	**0**	**1**	**0.1**	**-**
+ *Possible exposure in an HIV-endemic country*†	1	100	-	-	1	0.1	
Other/Unknown	**16**	**2.5**	**7**	**2.7**	**23**	**2.6**	**0.864**
Number of potential HIV exposures recorded							
1	446	70.4	151	59.0	597	67.1	
2	172	27.1	102	39.8	274	30.8	<0.001
3+	16	2.5	3	1.2	19	2.1	

* Sum of categories exceeds total sample size because participants may have ≥1 HIV exposure category reported in clinical file.
† *Possible exposure in an HIV-endemic country* is never assigned as a primary exposure category but is captured as an additional exposure category if an individual was born in, or spent considerable time living/working in an HIV-endemic country and experienced a potentially "risky" event.

3.5 Study strengths and limitations

Key limitations and challenges experienced throughout the development of the LHIV-Manitoba cohort, and the particular challenges associated with developing clinical cohorts using research dollars, have been described in detail elsewhere [167]. Briefly, a number participants expressed apprehension about the kinds of data that would be collected as a result of their involvement with the cohort, and in response, study staff made a point to spend adequate time to clearly explain the processes through which the study is able to link clinical and administrative data while maintaining confidentiality. Efficiently implementing study protocols without disrupting existing clinic operations was another substantial challenge; incorporating additional procedures related to cohort enrolment into routine encounters was difficult for healthcare providers who are working within busy HIV clinics. The study team regularly engages with providers to highlight the benefits that the cohort may confer to their own practice, their clients' needs, and the overall operations of Manitoba HIV Program.

Because enrolment protocols are clinic-based, this cohort may not be representative of people living with HIV who are sub-optimally engaged in care. As enrolment efforts move forward, it will be important for the study team to consider strategies to increase the proportion of participants belonging to demographic subgroups who are currently underrepresented in the cohort. It is of particular interest to the study team to understand whether certain subgroups are less likely to consent to cohort participation, and if so why. While findings from the cohort will still be important for informing care programming and policy decisions for the province, generalizability may be limited, and results must be interpreted accordingly. One key strategy to circumvent the misinterpretation of analyses derived from cohort data will be to involve Manitoba HIV Program clients and their providers in the analysis, interpretation, and knowledge

translation processes. Furthermore, given the passive, posthumous enrolment process for deceased participants, mortality among cohort participants is likely overestimated in the context of this study. More accurate mortality estimates could be derived using provincial administrative health datasets.

The LHIV-Manitoba cohort is the first comprehensive source of health data compiled from people living with HIV in the province and will provide important opportunities for systematically and comprehensively understanding clinical care needs, gaps, and outcomes of Manitobans living with HIV. Importantly, Manitoba is well-positioned to undertake large, population-based linkage studies given the existence of a single insurer (that is, MHSAL) that is responsible for payment of most health services, and the existence of linkable, population-based administrative health databases through the Manitoba Centre for Health Policy [168, 169]. The cohort also identifies common comorbidities such as diabetes and hypertension where further assessment of outcomes offers opportunities for targeted resource allocation for improved management. Furthermore, the Manitoba HIV Program embodies a unique care model—comprising both specialist and primary care services—that closely aligns with the Patient Centered Medical Home (PCMH) model of HIV care [170]. As such, findings from the LHIV-Manitoba cohort will be able to speak to the growing body of literature focusing on holistic models of HIV care delivery [170, 171].

Finally, because the clinical cohort is embedded within the Manitoba HIV Program, and stakeholders within MHSAL and the community of people with lived experience have been actively involved in its development, we also expect that data from the cohort will facilitate epidemiological analyses that can inform both HIV care programming and provincial policy on adequately resourcing HIV-related health services.

3.6 Future directions

Future analyses using clinical cohort data will focus on areas that have been identified as specific points of interest for the Manitoba HIV Program. Namely, developing a better understanding of the impact of existing provincial drug plans on clinical outcomes and exploring, for the first time in the province, characteristics and determinants of mortality among people living with HIV. Additionally, cohort data will be used to generate Manitoba-specific HIV care cascade estimates [4, 5, 16], which are presented in Chapter 4. Subsequent work will examine the local HIV care cascade through an equity lens (Chapter 5) to better understand how different groups of participants experience HIV care and treatment outcomes differently within Manitoba.

Preface to Chapter 4

Using clinical cohort data, Chapter 4details the methods used to develop an HIV care cascade model for the first time in Manitoba. A variety of possible indicator definitions, with differing stringencies, are presented as a way to add flexibility to the model that will allow it to be readily used in clinical practice, even in the absence of comprehensive data sources like the clinical cohort. Additionally, a final cascade model is presented using indicator definitions that were identified as the most programmatically relevant through an iterative consultation process with the medical directors of the Manitoba HIV Program.

The work presented in Chapter 4 was supported by collaborators in MSHAL's Information Management & Analytics unit—Aakash Amatya, Saila Parveen, and Faisal Shibley; the entire Manitoba HIV Program team; and Stella Leung at the Institute for Global Public Health, University of Manitoba. I was solely responsible for the conceptualization of the presented work, data analyses, and writing the original draft of the paper. Drs. Marissa Becker, Laurie Ireland, and Ken Kasper reviewed and provided critical feedback on the analyses and the paper.

Chapter 4. The HIV Care Cascade in Manitoba, Canada: Developing Methods, Measures, and Cross-Sectional Estimates to Meet Local Needs

Abstract

To date, little academic literature has focused on describing the epidemiology of HIV in Manitoba. Without a standardized system for the routine collection of clinical data from people living with HIV in the province it has not been possible to develop an HIV care cascade specific to Manitoba. This paper describes the steps and processes undertaken to develop a provincially relevant HIV care cascade model, establish the most appropriate measurements for each cascade step, and use local clinical data to derive local cascade estimates.

In 2013, a clinical cohort of people living with HIV was established as an embedded component within the Manitoba HIV Program. Using Manitoba-specific clinical cohort data (up to date as of December 31, 2017) to refine and contextualize nationally standardized cascade definitions, a set of cascade indicator definition options was created for each cascade step. These definitions were reviewed through an iterative process with providers from the Manitoba HIV Program to ensure local programmatic relevance, and then brought together to create a cascade model for Manitoba.

At the end of the 2017, 703 cohort participants were categorized in the *alive and diagnosed* step. Of those participants, 638 (90.8%) were classified as *in care*, 606 (86.2%) were *retained in care*, 573 (81.5%) were classified as *on treatment*, and 523 (74.4%) were

virologically suppressed. The greatest point of leakage between two consecutive steps in the cascade occurred between the first and second steps, where 9.3% of participants who were *alive and diagnosed* in 2017 were not *in care* in the same calendar year.

This is the first study to comprehensively examine clinical epidemiology of HIV in Manitoba using an HIV care cascade framework, thus meaningfully contributing to the limited body of academic literature focusing on HIV in the Canadian Prairies. Importantly, this work can inform programming to improve service coverage within the Manitoba HIV Program, and will contribute to the body of evidence used to inform provincial policies that will support the Manitoba HIV Program to do so.

4.1 Introduction

The HIV care cascade is a framework developed to examine and monitor individuals' engagement in, and utilisation of, a continuum of HIV-related health services and outcomes in the context of a particular health system—including HIV diagnosis, linkage to appropriate health services, initiation of effective treatment with ART, and ultimately, reaching virologic suppression. Early iterations of the HIV care cascade were developed with the primary purpose of illustrating the "ideal", albeit often over-simplified, care trajectory for people living with HIV, beginning from acquisition through virologic suppression [1, 4, 14, 42]. Over time, conceptualisations of the cascade have evolved to reflect real world complexities in providing and receiving HIV care, including cycles of engagement [3, 7, 10, 47], loss to clinical follow-up and mortality [45], and person-time spent in and between various cascade steps [39, 45, 67].

The cascade is a tool that can be used for monitoring and evaluating HIV treatment and care programs, particularly to identify gaps, bottlenecks, or limitations that exist within these programs [4, 5, 16, 56, 67, 172, 173], and to monitor the performance of health systems with respect to the provision of HIV-specific treatment and care services [30, 36, 56, 174]. At the national level, cascade frameworks are used for examining progress toward meeting high-level public health targets set out by global normative bodies, such as the WHO and UNAIDS, to minimize acquisition and transmission of HIV through strategies like the 90-90-90 initiative [50] and the 95-95-95 Fast-Track targets [175], or to reduce inequities in HIV incidence and prevalence through the Sustainable Development Goals [176]. Alongside these strengths, limitations to the programmatic utility of the cascade framework have also been highlighted. Researchers have noted the intensive data requirements to develop and maintain a programmatically useful HIV care cascade [7, 39, 46, 47, 69, 71], and the numerous challenges

in designing context-specific models that adequately capture complexities within HIV care trajectories [7, 42, 47, 67, 177]. Despite this, the simplicity and intuitive design of the traditional cascade model [7] render it a helpful framework for examining overall trends in the provision and utilisation of HIV care.

4.1.1 HIV in Manitoba: Background and local context

Manitoba is a central Prairie province in Canada with unique HIV epidemiological trends and annual rates of new HIV infections consistently higher than the national average [17, 20-22]. While the majority of prevalent HIV infections in Canada are attributable to condomless anal sex between men [17, 21, 22], transmission in Manitoba is disproportionately attributed to condomless vaginal sex [24, 159]. As a result, in 2018, the proportion of new infections among women in Manitoba (40.0%) [24] was disproportionately high in relation to the rest of the country (29.3%) [17]. Currently, surveillance reports published by the PHAC and MSHAL are the primary sources of HIV epidemiological data in Manitoba [17, 24, 159]. These reports provide descriptive epidemiological analyses of the previous year's new HIV infections but are limited in their ability to shed light on patterns and trends in HIV care and service delivery in the province. Furthermore, without a system in place to routinely collect individual-level clinical data from people living with HIV in the province and because relevant, available datasets have not been collected nor stored in a single database, in the past, it had not been possible to develop a Manitoban HIV care cascade.

In 2013, a prospective clinical cohort of people living with HIV in Manitoba was established with the support of a federally funded program of research, the LHIV study. The development and profile of the LHIV-Manitoba clinical cohort has been described in detail elsewhere (Chapter 3). Briefly, at the end of the first quarter in 2019, 890 unique individuals

were included in the cohort. Any adult (≥18 years) living with HIV in Manitoba, or receiving HIV care in the province, were eligible for participation in the cohort, with the exception of individuals who were under the jurisdiction of the Public Guardian and Trustee of Manitoba or were otherwise unable to make decisions pertaining to their own healthcare. A complete clinical dataset exists for 725 (81.5%) cohort participants who agreed to have their data reviewed and extracted from clinical records within the Manitoba HIV Program. A limited clinical dataset exists for an additional 165 individuals whose clinical records were reviewed posthumously. Importantly, the cohort has been developed as an embedded research project within the Manitoba HIV Program—the primary provider of care for people living with HIV in the province—in order to ensure that findings derived from research using the cohort will have direct programmatic and clinical relevance (Chapter 3).

Given the heterogeneity of the HIV epidemic across Canada [17, 20], understanding how HIV care cascades differ across provinces and in different contexts is essential in ensuring that the implementation of local HIV health services and clinical HIV care programs are effective and appropriately tailored to the needs of the population served. This paper describes the steps and processes undertaken to develop an HIV care cascade model for Manitoba, establish the most appropriate measurements for each cascade step, and use clinical data from the LHIV-Manitoba cohort to derive local cascade estimates. The establishment of this cascade will enable the Manitoba HIV Program, MHSAL, and other decision-makers in Manitoba to better understand where bottlenecks or leakages [5] may be occurring in the continuum of HIV care in Manitoba, and can assist in identifying potential points of programmatic or policy intervention to ensure that health system in Manitoba is providing effective coverage of care services for people living with HIV in the province.

4.2 Methods

Before generating estimates for a Manitoba-specific HIV care cascade, it was necessary to establish clear, locally relevant definitions for each cascade step and to consider all potential data sources for developing a comprehensive cascade for the province.

In 2013, the Surveillance and Epidemiology Division of PHAC convened a National HIV Cascade Working Group with the intention of developing a Canadian HIV care cascade using existing, available data from provincial and territorial jurisdictions [124]. The Working Group, which had representation from HIV service providers and/or researchers working in seven provinces and one territory, as well as representatives from Correctional Service of Canada and PHAC, was tasked with developing standardised definitions for each cascade step. Through a consultation process spanning nearly three years, PHAC engaged clinicians, researchers, and representatives from provincial/regional public health units to identify existing data sources in each jurisdiction that could be used to measure cascade indicators. By mid-2016, the Working Group had developed primary and supplementary definitions for four core steps of the HIV care cascade based on data that are routinely collected and readily available across all provincial and territorial jurisdictions: *linked to care*, *retained in care*, *on treatment*, and *virologically suppressed* [178].

Building upon the definitions developed by the Working Group, we set out to develop cascade indicator definitions that specifically consider the data available in Manitoba and the clinical and programmatic context in which HIV care is provided in the province.

4.2.1 Data sources

Developing definitions using a readily available data source like the clinical cohort ensures that the Manitoba HIV Program will be able to easily re-calculate cascade estimates, as needed, for programmatic decision-making. The LHIV-Manitoba clinical cohort was the sole source of data from which cascade indicator definitions were developed and cascade estimates were derived. Data from all clinical cohort participants were considered for inclusion in analyses to develop the Manitoban HIV care cascade. Participants who were not alive as of December 31, 2017; and/or had not been diagnosed with HIV as of December 31, 2017; and/or did not provided consent to have their clinical data reviewed *and* linked to provincial administrative health databases were excluded from analyses (Figure 4.1). All data were current up to December 31, 2017. A comprehensive overview of the datasets included in the clinical cohort is provided in Appendix CIn short, the cohort includes data collected from participants' clinical records individually linked to de-identified provincial administrative health databases housed at MHSAL, the primary provider of health insurance and the payer of nearly all health services in in the province. A complete description of cohort participants' characteristics is presented in Chapter 3.

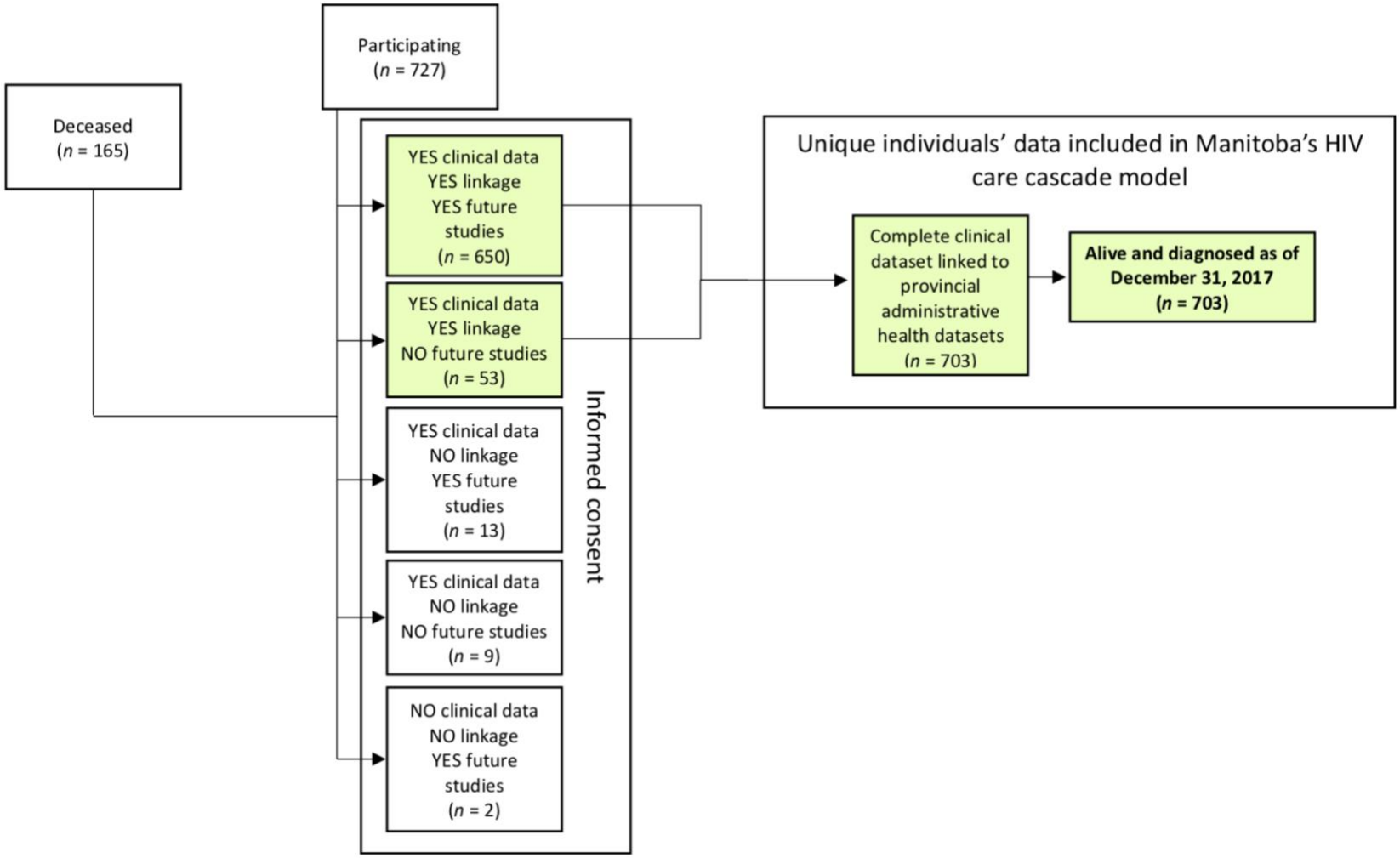

Figure 4.1. Sample selection criteria for the development of the Manitoban HIV care cascade.

Quantitative plasma viral load, CD4 cell count testing data, records of physician visits, and drug dispensation data were used to develop indicator definitions. All viral load tests in Manitoba are conducted at the Cadham Provincial Laboratory (CPL) [179] and results are captured in MHSAL's provincial administrative databases. Similarly, the Drug Program Information Network (DPIN) database, which provides individual-level drug dispensation data for Manitoba residents from all community pharmacies in the province [180], is linked to clinical data in the cohort via provincial administrative health databases. Individual-level data on participants' ambulatory physician visits were identified using medical claims (captured through physician billings) associated with HIV-related International Classifications of Disease (ICD)-9 and/or ICD-10 codes. In Manitoba, CD4 cell counts conducted in laboratories are entered directly into medical records (electronic or paper files) within the Manitoba HIV Program. CD4 cell count data for each cohort participant are manually abstracted and entered into the clinical cohort database on a biannual basis (Chapter 3).

4.2.2 Cascade indicator definition development

A key purpose for developing this cascade was to inform HIV care programming and policies around the provision of HIV care in Manitoba. The PHAC Cascade Working Group's consensus definitions provided a useful starting point upon which to develop definitions for provincial cascade step indicators. However, in order to ensure local relevance and programmatic applicability, indicator definitions were further refined through an iterative review process with providers from the Manitoba HIV Program.

Given that the cascade was developed using cross-sectional cohort data, rather than real-time longitudinal data, the first step of our model comprises all cohort participants who were alive and had received a positive HIV diagnosis by the end of the 2017 calendar year. For each

subsequent cascade step, two to three indicator definitions were developed using different degrees of stringency (lenient, moderate, or conservative) in their numerator as a way to examine the sensitivity of our estimates (Box 4.1). Additionally, the *virologically suppressed* indicator was also assessed using alternative denominator definitions that either included all people categorized as *retained in care* or all people defined as *on treatment*, while the *in care* and *retained in care* indicator definitions were also examined with and without the inclusion of physician visit data.

In order to assess sensitivity of numerator definitions for each cascade step indicator, crude estimates were developed for each cascade step in which the denominator of each indicator comprised all individuals defined as *alive and diagnosed*. Because the estimate of each subsequent indicator is contingent upon the estimate of the previous indicator, decisions for each indicator definition were made in a stepwise fashion. That is, the *retained in care* step is calculated as a proportion of the total number of people who meet the definition of the *in care* step. As such, before identifying the most appropriate definition for the *retained in care* step, a decision had to be made about the most appropriate definition for the *in care* step first.

Estimates derived for crude cascade step indicators, using all possible numerator definitions, were reviewed by the first and last authors and a short list of indicator definition options was created. The shortlist of indicator definitions was then presented to the two medical directors of the Manitoba HIV Program, who are also practicing HIV clinicians, to finalize definitions that would be used for the Manitoba HIV care cascade.

Box 4.1. Indicator definition options for each HIV care cascade step using clinical cohort data.

ALIVE AND DIAGNOSED	
Definition	Alive and diagnosed with HIV on or before December 31st, 2017.
IN CARE	
Among *alive and diagnosed*…	
Conservative definition	At least 1 viral load test or CD4 count ± physician visit for HIV within the first 90 days of 2017 (or within 90 days of diagnosis, if diagnosed within calendar year).
Moderate definition	At least 1 viral load test or CD4 count ± physician visit for HIV within the first 180 days of 2017 (or within 180 days of diagnosis, if diagnosed within calendar year).
Lenient definition	At least 1 viral load test or CD4 count ± physician visit for HIV in 2017.
RETAINED IN CARE	
Among *in care*…	
Moderate definition	At least 2 viral load tests ± physician visits for HIV, at least 90 days apart, in 2017.
Lenient definition	At least 2 viral load tests ± physician visits for HIV in 2017.
ON TREATMENT	
Among *retained in care*…	
Conservative definition	At least 3 antiretroviral drug (ARV) dispensations, at least 90 days apart, in 2017.
Moderate definition	At least 2 ARV dispensations, at least 90 days apart, in 2017.
Lenient definition	At least 1 ARV dispensation in 2017.
VIROLOGICALLY SUPPRESSED	
Among *on treatment*…	
Conservative definition	At least 2 viral load test results below 200 HIV RNA copies/mL in 2017, one of which is the last viral load test in the calendar year.
Moderate definition	At least 2 viral load test results below 200 HIV RNA copies/mL in 2017.
Lenient definition	Last viral load test result in 2017 is below 200 HIV RNA copies/mL.
Among *retained in care*…	
Conservative definition	At least 2 viral load test results below 200 HIV RNA copies/mL in 2017, one of which is the last viral load test in the calendar year.
Moderate definition	At least 2 viral load test results below 200 HIV RNA copies/mL in 2017.
Lenient definition	Last viral load test result in 2017 is below 200 HIV RNA copies/mL

4.3 Ethics approvals

This study received approval from the UM-HREB (ethics no. HS21678). The larger LHIV-Manitoba cohort study, to which this study is linked, received approvals from UM-HREB (ethics no. HS15817), the local hospital's Research Impact Committee, HIPC of MHSAL, and the Nine Circles Community Health Centre Research Committee. This work has also received support from the Health Information Research Governance Committee of *Nanaandawewigamig*, the First Nations Health and Social Secretariat of Manitoba.

4.4 Results

4.4.1 Deriving estimates for each HIV care cascade indicator definition option

Examining crude estimates for each cascade step—that is, eliminating the requirement that an individual must be categorized in an earlier cascade step in order to be included in a subsequent step—allowed us to assess how changes in numerator definitions alone influenced each cascade step (Figure 4.2).

In total, 703 cohort participants were categorized as *alive and diagnosed* as of December 31, 2017. The number of participants defined as *in care* ranged from 386 (conservative definition without physician visit data) to 663 (lenient definition, including physician visit data). Supplementing *in care* definitions with physician visit data increased crude estimates for all definition stringencies, but these differences decreased as definitions became less stringent. Crude estimates for the *retained in care* indicator ranged from 548 (moderate definition, excluding physician visit data) to 631 (lenient definition, including physician visits), and again, the inclusion of physician visit data increased crude estimates, regardless of definition stringency. Crude estimates of the number of participants *on treatment* and *virologically*

suppressed increased as definition stringency decreased, from 584 to 630 and 487 to 574, respectively.

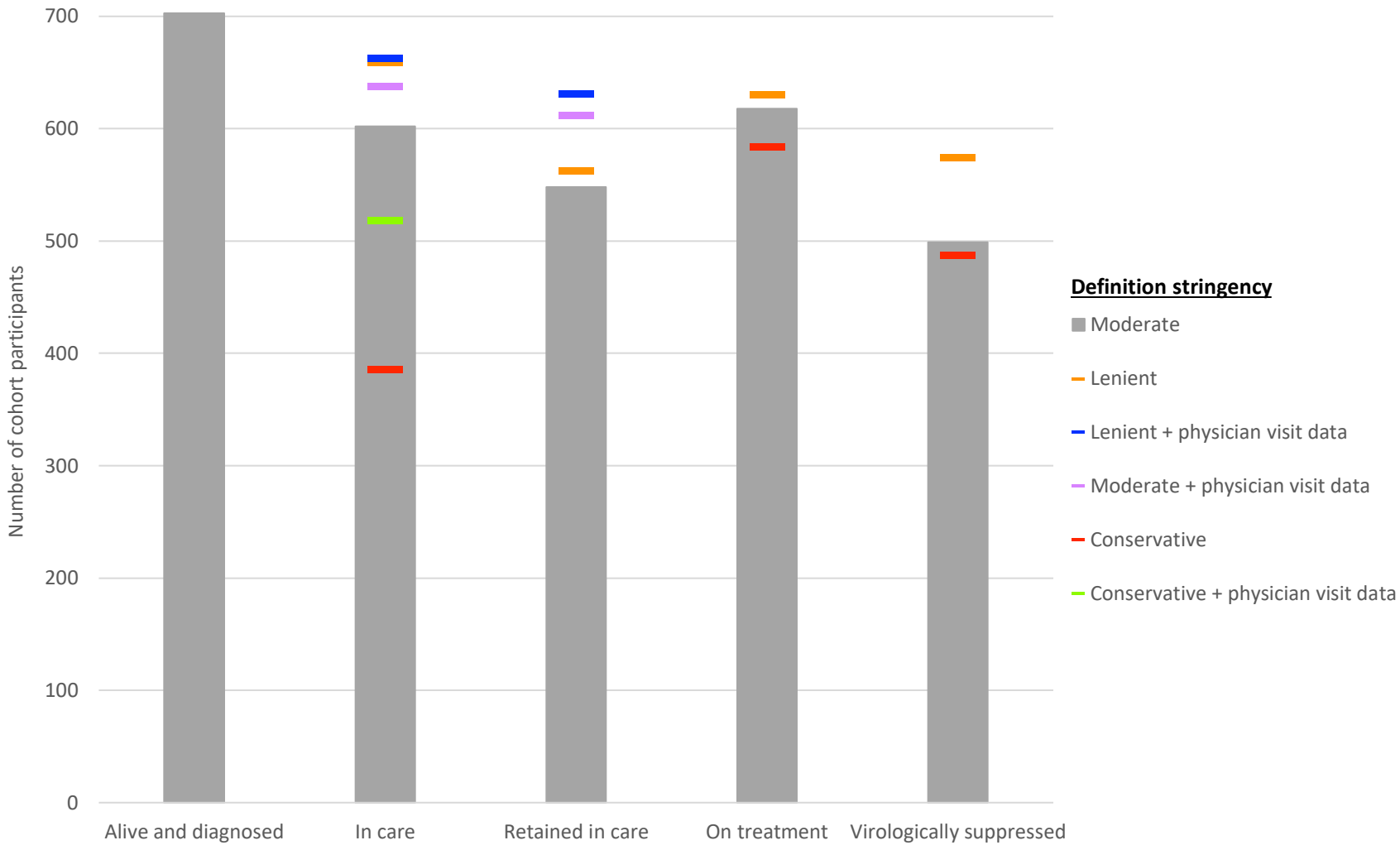

Figure 4.2. Crude estimates for total number of cohort participants in each cascade step among all *alive and diagnosed*, as of December 31, 2017. Coloured markers indicate variation in cascade step estimates with changes in data sources and indicator definition stringency.

4.4.2 Establishing the final HIV care cascade model for Manitoba

Through consultation with the Manitoba HIV Program and prioritizing programmatic utility, it was decided that, when possible, including physician visit data in all relevant indicator definitions was preferable. Figure 4.3 illustrates the final HIV care cascade model, which was developed using indicator definitions deemed most appropriate and programmatically useful. Moderate definitions that included physician visit data (indicated by purple markers in Figure 4.2) were selected as the final definitions for the *in care* and *retained in care* cascade steps. The moderate definition of the *on treatment* step (indicated by grey bar in Figure 4.2) was identified as most appropriate and the lenient definition of *virologically suppressed* (indicated by orange marker in Figure 4.2) was determined to be the most programmatically useful.

At the end of the 2017, of the 703 cohort participants in the *alive and diagnosed* step, 90.8% were classified as *in care*, 86.2% were *retained in care*, and 81.5% were classified as *on treatment* (Figure 4.3). The final HIV care cascade model includes two versions of the *virologically suppressed* step. The first is a more conventional depiction of the number of virologically suppressed participants as a proportion of those *on treatment* (74.4%), while the alternative version of the final cascade step represents those suppressed as a proportion of those *retained in care* (76.2%). The magnitude of difference between the first and second versions of the *virologically suppressed* step is not large (523 vs. 536, respectively). However, the alternative version of the final cascade step (that is, expressing this final cascade step as a function of those *retained in care*) importantly highlights the proportion of individuals who maintain a suppressed viral load (<200 copies/mL) either without treatment—for example, in the case of viremic- or elite controllers [181]—or with adherence to treatment that does not meet the criteria of our definition.

The greatest point of "leakage" between two consecutive steps in the care cascade is observed from the first to second step (Figure 4.3); 9.3% of participants who were *alive and diagnosed* in 2017 were not *in care* in the same calendar year. However, when considering those *virologically suppressed* as a proportion of those *retained in care*, the cascade shows a 10.0% loss in participants between those steps. Among cohort participants who were *in care*, the majority (95.5%) were also *retained in care*, and once retained, 95.3% were also *on treatment*.

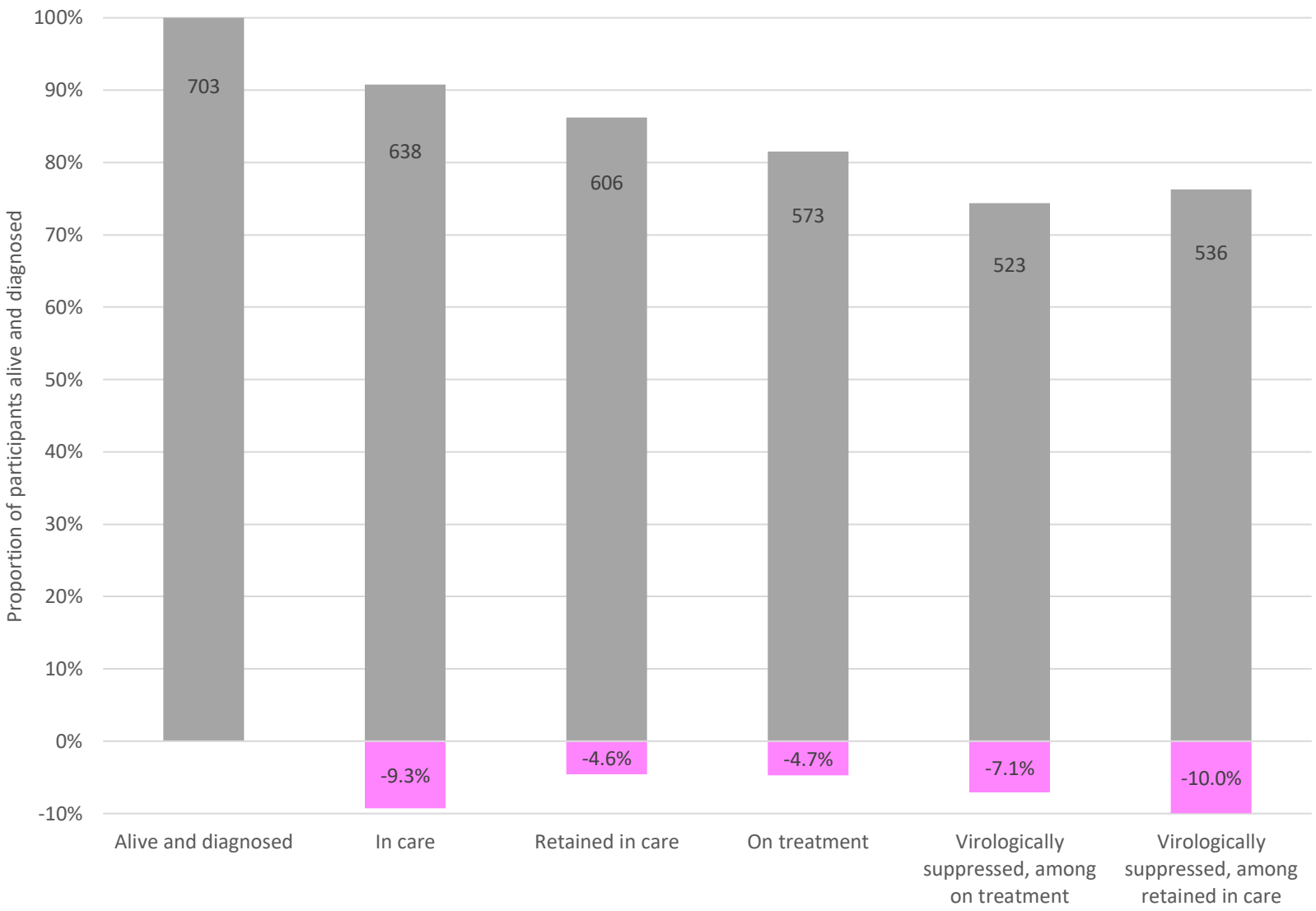

Figure 4.3. HIV care cascade, including the proportion of individuals lost from the previous cascade step (pink). Each step represented as a proportion of the total number of participants alive and diagnosed as of December 31, 2017.

4.5 Discussion

This is the first study to comprehensively examine clinical epidemiology of HIV in Manitoba using an HIV care cascade framework, thus meaningfully contributing to the limited body of academic literature focusing on HIV in the Canadian Prairies. Haber and colleagues [46] identify numerous attributes of an "ideal" HIV care cascade. First, the authors suggest that a cascade should, ideally, be created using data based on a single population and should be both denominator-denominator linked (that is, data for the same individuals are assessed for each cascade step) and denominator-numerator linked (that is, individuals are only eligible to be counted in the numerator of a step if they are also included in the denominator of the *same* step)—all three criteria that we have been able to meet using data from the clinical cohort. Using the clinical cohort data to generate cascade estimates provides the unique opportunity to examine patterns and trends in HIV care utilization in the province over time. Although the present study presents only cross-sectional analyses, as the cohort matures and subsequent years of data are added, we will also be able to examine the cascade longitudinally—another desirable attribute of an "ideal" cascade [46]. Longitudinal datasets are perceived to be superior for building cascade models because they incorporate less bias than cross-sectional data and allow for survival analyses, which are important for tracking individuals' movement through the cascade. Survival analyses are also important for illuminating patterns of churn, delays, or timely progression between steps [45, 46], which can provide insight into whether HIV care programs are meeting the needs of their clients [45]. Previous work also highlights the need to place more emphasis on evaluating late entry into each cascade step [39] and to better understand churn within and across cascade steps [3, 11, 42, 47].

Importantly, this study has the potential to inform the development of provincial policies that will support the Manitoba HIV Program, in supporting clients' needs to facilitate earlier linkage to and optimal engagement in care. More specifically, examining Manitoba's HIV care cascade, and understanding limiting factors within it, can provide the Manitoba HIV Program with clear targets for programmatic intervention. Considering the UNAIDS 90-90-90 targets as relevant markers for optimal progress along the HIV care cascade, our findings (Figure 4.3) highlight that the proportion of cohort participants (all of whom are diagnosed with HIV) who were *on treatment* missed the 90% target, at 81.5% (n = 573/703). Currently, Manitoba does not have a universal drug plan, resulting in notable disparities in out-of-pocket expenses for people who choose to be on treatment. Preliminary analyses of cohort data suggest that out-of-pocket drug expenses are incurred differently by different demographic groups in Manitoba [182], highlighting the importance of gaining a clearer understanding of how policy changes that support barrier-free access to treatment and care for people living with HIV may be able to positively influence the local HIV care cascade. The present study also shows that in 2017, the last 90-90-90 target was achieved, with 91.3% (n = 523/573) of cohort participants who were *on treatment* also reaching *virologic suppression*. Future work will examine how the cascade differs across different socio-demographic subgroups within our cohort population.

Another goal of this study was to develop an adaptable and easy-to-use cascade framework that can be regularly updated within the Manitoba HIV Program as a way to monitor program performance and identify stages throughout the cascade at which individuals are "lost" to care. We have developed a range of indicator definitions that can be used to populate a locally relevant cascade model with reasonable and programmatically useful estimates, even if available data are limited to those obtained in clinical records. Using the cohort data allows for access to

administrative health datasets that are not always readily available to clinical programs, and it may be more feasible for the Manitoba HIV Program to rely on viral load test results and/or CD4 cell count data as proxies for the *in care* and the *retained in care* steps retention in HIV care among program clients. Previous work has highlighted limitations to relying on laboratory data as a proxy for actual clinic attendance [71, 183], particularly that it generates relatively conservative estimates for the *in care* and *retained in care* cascade steps. However, by creating indicator definitions with various levels of stringency, our model allows users to compensate for such data limitations by adjusting stringency accordingly. For example, in the absence of physician visit data to complement laboratory data for the in care and retained in care steps, using lenient definitions may bring estimates closer to estimates that we would expect to see with a more comprehensive dataset with multiple and different sources (Figure 4.2).

4.5.1 Study strengths and limitations

While this study has numerous important implications for Manitoba, it is worth noting that the cascade presented here is limited in a number of ways. Our reliance on clinical cohort data means that we cannot guarantee generalizability of the cascade results to the population of people living with HIV in Manitoba, although previous work indicates that characteristics of cohort participants are reasonably representative of the larger Manitoba HIV Program clinic population (Chapter 3). Further, because recruitment into the clinical cohort employed a clinic-based opt-in approach, it is likely that this cascade over-estimates engagement in HIV care in Manitoba. Finally, using the cohort as a starting point for the first step of the cascade means that we are not able to ascertain information about the diagnosed and undiagnosed fractions among all people living with HIV in Manitoba.

A particular strength of this work lies in our consideration and incorporation of the experiential knowledge held by service providers within the Manitoba HIV Program in the development of the cascade step indicator definitions. Embedding a research element into existing HIV care programs provides opportunities to monitor and evaluate program activities, identify gaps in programming, and develop adaptive responses to improve program effectiveness and ensure delivery of quality services [142, 143]. Involving providers in the cascade development process enhances the usefulness and applicability of each cascade step definition and familiarizes the Manitoba HIV Program with the potential opportunities to use program data to generate knowledge that can be used to assess, modify, and enhance service delivery, and inform provincial policies related to the provision of HIV-related service, including strategies for testing and surveillance.

Preface to Chapter 5

Finally, the study presented in Chapter 5engages in a more nuanced analysis of the HIV care cascade, thus building upon analyses presented in Chapter 4. Here, an "equity lens" is applied to the cascade in order to examine how individuals within different sociodemographic groups proceed through the continuum of HIV care services provided through the Manitoba HIV Program, and to determine whether certain characteristics are associated with (sub)optimal engagement in HIV care in the province. This work aims to broaden and contextualize the current understanding of health service coverage among people living with HIV in Manitoba and to call attention to inequalities that exist across the local HIV care cascade among clinical cohort participants.

I conceptualized the study in Chapter 5, conducted all analyses, and wrote the first draft of the paper. Drs. James Blanchard and Marissa Becker reviewed and provided critical feedback on the analyses, data visualization techniques, and the draft paper.

Chapter 5. *Leaving no one behind?* An Equity Profile of the HIV Care Cascade in Manitoba, Canada

Abstract

Manitoba is a central Canadian province with annual rates of new HIV infections that are consistently higher than the national average. HIV surveillance statistics and data from the provincial HIV care program suggest that epidemiological heterogeneity exists across Manitoba, with new HIV cases disproportionately reported among females, individuals identifying as Indigenous, and those with a history of injection drug use. Given the observed heterogeneity in HIV acquisition, it is of interest to understand whether this translates into inequalities in HIV care across the province.

Using cohort data (described in Chapter 3) and the previously established HHIV care cascade model for Manitoba (described in Chapter 4), Chapter 5 presents disaggregated analyses of the cascade that identify inequalities in service coverage and clinical outcomes among different groups receiving HIV care in Manitoba. The equity analyses in this study include equiplots to visualize absolute inequalities across the cascade and multivariable logistic regression models to examine associations between sociodemographic variables and likelihood of reaching each cascade step.

The presented equity analyses highlight substantial variation in engagement in and coverage of HIV-related health services among clinical cohort participants. Being older, white, a non-immigrant, and reporting no history of injection drug use were all associated with better

engagement in the HIV care cascade in comparison to their counterfactuals. Visualizing data with equiplots was found to be particularly useful; they illuminated numerous inequalities across the cascade that, though not statistically significant in multivariable models, are nonetheless critical to consider for programming aimed at minimizing inequities in service delivery.

Together with future research that focuses on understanding *why* inequalities exist across the HIV care cascade in Manitoba, the equity analyses presented in this study can provide the Manitoba HIV Program with evidence to inform the development of patient-centred care plans that meet the needs of diverse client subgroups, and to advocate for policy changes that support and facilitate more equitable HIV care across the province.

5.1 Introduction

At the end of 2018, PHAC estimated that 88,881 people were living with HIV in the country, with a total of 2,561 people newly diagnosed in the same year [17]. Nationally, new HIV diagnoses are disproportionately reported among Indigenous populations [17, 22] and people who have immigrated from "HIV endemic" countries [22]. Furthermore, in 2018, prevalent HIV infections in Canada were primarily attributable to condomless anal sex between men (41.4%) and condomless vaginal sex (32.3%) [17].

Manitoba is a central Canadian province where annual rates of new HIV infections are consistently higher than the national average (7.9 vs. 6.9 per 100,000 population, respectively, in 2018) [17]. Injection drug use (33.9%), condomless anal sex between men (24.4%), and condomless vaginal (heterosexual) sex (20.9%) are the most commonly identified HIV risk exposures in the province [23]. New HIV infections were disproportionately high in Manitoba, compared to the rest of Canada, among individuals identifying as Indigenous (50% vs. 19.3%) and among females (40% vs. 29.3%) [17, 24]. Furthermore, notable heterogeneity in rates of new HIV infection exists across the province by geography, age, and sex [24]—in 2018, 77.6% of new diagnoses occurred in Winnipeg, the provincial capital and main urban centre, and among newly diagnosed females, 11.6% were ≤19 years (compared to 1.6% of males) and 14.0% were ≥60 years (compared to 3.1% among males) [24].

Over the past decade, the field of HIV research has placed heavy emphasis on the HIV care cascade—a framework and analytic tool that provides insights into the continuum of care services for people living with HIV within a particular context [1, 46, 99, 140]. Conventionally, cascades use aggregate data to illustrate the proportion of individuals in a given population of people living with HIV who have been diagnosed, linked to HIV care services, retained in care,

then initiated and sustained on HIV treatment to, ultimately, reach virologic suppression. Using aggregate data to construct a picture of the continuum of HIV care for an entire population is useful insofar as it can provide a general picture of points of "leakage" or "bottlenecks" existing within a health system or care program. However, relying on aggregate data to paint a picture of an entire population risks obscuring the underlying heterogeneity among and between individuals and groups who make up the population. In order to develop interventions and programs that address inequities in HIV care among subgroups, it is crucial to conduct additional, disaggregated analyses that showcase the nuances within a population and highlight inequalities across the cascade steps.

In 2015, all 193 Member States of the United Nations (UN) agreed upon the 2030 Agenda for Sustainable Development, comprising seventeen Sustainable Development Goals (SDGs), which build upon the Millennium Development Goals (MDGs) introduced fifteen years earlier [133]. At the core of the SDGs is the notion of *leaving no one behind*, which:

> represents the unequivocal commitment…to eradicate poverty in all its forms, end discrimination and exclusion, and reduce the inequalities and vulnerabilities that leave people behind and undermine the potential of individuals and of humanity as a whole [184, p. 6].

This idea underscores the interconnectedness of the SDGs and principles of health equity [132]—a noted limitation of the MDGs [139]. As such, under the purview of the SDGs [135], there is a need for research that focuses on identifying (health) inequalities that exist, examining the factors that perpetuate and exacerbate these inequalities, and ultimately, developing strategies to minimize or, ideally, eliminate them. As noted in SDG 17, to adequately assess (in)equities, it

is necessary that data are disaggregated by socioeconomic, demographic and other relevant, context-specific characteristics [135, 139].

Publicly available HIV epidemiological data in Manitoba are limited to reports published by PHAC [17] and MHSAL [24], which focus solely on surveillance data. As such, local understandings of inequalities in HIV care and clinical outcomes among different groups of people living with HIV in the province are rudimentary. In 2013, a prospective clinical cohort of people living with HIV in Manitoba was established as a part of a larger program of research funded by the Canadian Institutes of Health Research (Chapter 3). The establishment of this cohort opens up numerous analytic opportunities to better understand HIV epidemiology in Manitoba and, for the first time, provides access to de-identified, individual-level clinical data, allowing for disaggregated analyses to take place. Here, using cohort data and building upon previous work (Chapter 4), we present disaggregated cascade analyses that importantly identify inequalities in service uptake and clinical outcomes among different groups receiving HIV care in Manitoba. In conjunction with future research to understand *why* identified inequalities exist across the cascade [140], this examination of the care cascade through an "equity lens" will provide the Manitoba HIV Program with evidence needed to strategize and develop patient-centred care plans that meet the needs of heterogeneous client subgroups, and to advocate for policy changes that address inequities in HIV care across the province.

5.2 Methods

5.2.1 Study setting

Manitoba has a population of 1.36-million people, spanning over 550,000 square kilometres [185]. Approximately 57% of Manitoba's population lives in the capital city of Winnipeg, 37% in the western, eastern, and southern regions (rural), and 6% in the north (rural-

remote) [186]. HIV care in Manitoba is primarily provided through the Manitoba HIV Program, comprised of three clinics—two in Winnipeg and one in a mid-sized rural city in southern Manitoba (refer to Figure 3.1) [187]. As such, the majority of Manitoba HIV Program clients living in rural and rural-remote regions of the province are required to travel substantial distances to attend a clinic. The Manitoba HIV Program employs a multidisciplinary care model encompassing a full complement of health and social service providers, including HIV specialists and family physicians, registered nurses, nurse practitioners, pharmacists, social workers, and a number of other allied health professionals. Despite Canada's publicly funded healthcare system, none of the Canadian provinces or territories have a single drug plan that provides universal coverage for all of its citizen, and out-of-pocket expenses associated with prescription medications vary substantially depending on an individual's insurance coverage [188]. Indeed, previous analyses using data from our clinical cohort highlight notable inequalities in out-of-pocket medication expenses exist for people living with HIV who choose to be on treatment [182].

5.2.2 Data sources

Data used to generate the disaggregated care cascades presented here are derived from the clinical cohort dataset, comprising individual-level, de-identified clinical data linked to provincial administrative health datasets, which are current through December 31, 2017. The process of establishing the cohort, a complete profile of cohort participants, and a comprehensive description of the datasets, including the variables contained within them, are detailed in our earlier work (Chapter 3). In brief, as of March 31, 2019, the cohort comprised 890 unique individuals. All adults (≥18 years) living with HIV and/or receiving HIV care in Manitoba were eligible for participation, except for individuals who are under the jurisdiction of the Public

Guardian and Trustee of Manitoba or are otherwise unable to make their own healthcare decisions. A complete dataset exists for 725 cohort participants (81.5%) who agreed to have their data extracted from clinical records and anonymously linked to administrative health databases, and a limited dataset exists for an additional 165 individuals whose records were reviewed posthumously (Figure 3.2). Importantly, the clinical cohort has been developed as an embedded research project within the Manitoba HIV Program in order to ensure that findings derived from research using the cohort will have direct programmatic and clinical relevance.

All cohort participants who provided informed consent to have their clinical data reviewed and linked to administrative health datasets, were alive and had received a positive HIV diagnosis as of December 31, 2017 were included in the baseline HIV care cascade model and subsequent equity analyses (refer back to Figure 4.1).

5.2.3 Equity analyses

An HIV care cascade model has previously been developed and specifically tailored to accommodate available data sources within Manitoba (Chapter 4). Box 5.1, below, outlines the established definitions for the five indicators representing each step of the Manitoban HIV care cascade.

Box 5.1. Final indicator definitions for the Manitoban HIV care cascade model.

CASCADE STEP	DEFINITION
Alive and diagnosed	Cohort participants who were alive and diagnosed with HIV on or before December 31st, 2017.
In care	Among those *alive and diagnosed*: Cohort participants who had at least 1 viral load test, at least 1 CD4 count, and/or at least 1 physician visit for HIV within the first 180 days of 2017 (or within 180 days of HIV diagnosis, if diagnosed in 2017).
Retained in care	Among those *in care*: Cohort participants who had at least 2 viral load tests and/or at least 2 physician visits for HIV, at least 90 days apart, in 2017.
On treatment	Among those *retained in care:* Cohort participants who had at least 2 antiretroviral drug dispensations, at least 90 days apart, in 2017.
Virologically suppressed	Among those *on treatment:* Cohort participants whose last viral load test result in 2017 was below 200 HIV RNA copies/mL.

To examine inequalities across the Manitoban care cascade, we identified relevant "equity variables" available within the cohort by which each cascade step indicator was then disaggregated. These variables—which have been recommended for use in equity analyses previously [132, 139, 189]—included age; sex; geographic location of residence; self-identified ethnicity; immigration status; and primary HIV exposure category, identified using a "risk hierarchy" framework [164]. Participants' geography is categorized by provincial Regional Health Authority (Figure 5.1), which is inferred from the six-digit postal code of residence at time of cohort enrolment, as recorded in the cohort database [190]. An individual's immigration status is categorized based upon whether they are foreign-born and had immigrated to Canada after 2001[v], versus those who are Canadian-born or participants who had immigrated to Canada prior to 2001.

[v] The 2001 cut-off is based upon the year in which the policy for mandatory HIV screening was introduced in the Immigration Medical Exam. See report by Klein, 2001: http://www.aidslaw.ca/site/wp-content/uploads/2013/04/ImmigRpt-ENG.pdf.

Figure 5.1. Schematic map of health regions in Manitoba. Adapted from Manitoba Health, Seniors and Active Living.

To aid in the visualization of these equity analyses, equiplots [192] were used to illustrate the absolute inequalities in reaching each cascade step among clinical cohort participants with different sociodemographic characteristics and HIV risk exposures. Equiplots were generated in Stata 15.1 (College Station, TX) using code freely available through the International Centre for Equity in Health, Universidad Federal de Pelotas, Brazil [192].

Subsequently, four multivariable logistic regression analyses were run, one each using the *in care*, *retained in care*, *on treatment*, or *virologically suppressed* cascade steps as the binary dependent variable. The key "equity variables" were included in each model as independent and control variables. All categorical equity variables were converted to dummy variables in the model; age was included as a continuous variable. All independent variables were tested for collinearity prior to inclusion in the model. Crude and adjusted odds ratios (AOR) are presented using 95% confidence intervals (95%CI) to assess statistical significance. All statistical analyses were performed using Stata 15.1 (College Station, TX).

5.3 Ethics approvals

This work received approval from UM-HREB (HS21678). The larger cohort study in which this work is embedded received approvals from UM-HREB (HS15817), the local hospital's Research Impact Committee, HIPC of MHSAL, and the Nine Circles Community Health Centre Research Committee. The cohort study has also received support from the Health Information Research Governance Committee of *Nanaandawewigamig*, the First Nations Health and Social Secretariat of Manitoba.

5.4 Results

In total, 703 cohort participants were alive and diagnosed with HIV by the end of 2017. Relevant characteristics of these participants are outlined in Table 5.1.

Among those *alive and diagnosed*, 90.8% met the definition of *in care*, 86.2% were *retained in care*, and 81.5% were *on treatment*, and nearly three-quarters (74.4%, $n = 523$) of cohort participants had reached the *virologically suppressed* stage of the cascade by the end of 2017 (Figure 5.2).

Table 5.1. Select sociodemographic characteristics and HIV risk exposures among clinical cohort participants (N = 703).

	n	**%**
Age range (years)		
18-29	41	5.8
30-39	127	18.1
40-49	200	28.5
50-59	233	33.1
60+	102	14.5
Mean (SD)	48.5 (11.5)	
Median (IQR)	49.3 (15.6)	
Sex		
Male	507	72.1
Female	196	27.9
Geography (by region)		
Winnipeg	576	81.9
Northern Manitoba	25	3.6
Western Manitoba	25	3.6
Eastern Manitoba	44	6.3
Southern Manitoba	27	3.8
Out of province	6	0.9
Ethnicity		
White	307	43.7
Indigenous	269	38.3
Sub-Saharan African/Caribbean/Black	91	12.9
Other*	36	5.1
Immigration status†		
Non-immigrant	613	87.2
Immigrant	90	12.8
HIV exposure category		
Condomless anal sex between men (MSM) only	243	34.6
MSM + injection drug use (IDU)	20	2.8
IDU only	110	15.7

	n	%
Condomless vaginal (heterosexual) sex	310	44.1
No identified risk/Other risk‡	20	2.8

* Includes Latin American, East/Southeast Asian, South Asian, West Asian/North African/Middle Eastern.
‡ "Other risk" includes recipient of blood/blood products, perinatal acquisition, occupational exposure
† "Immigrant" includes foreign-born participants who immigrated to Canada in 2001 or later. "Non-immigrant" includes Canadian-born participants and foreign-born participants who immigrated to Canada prior to 2001.

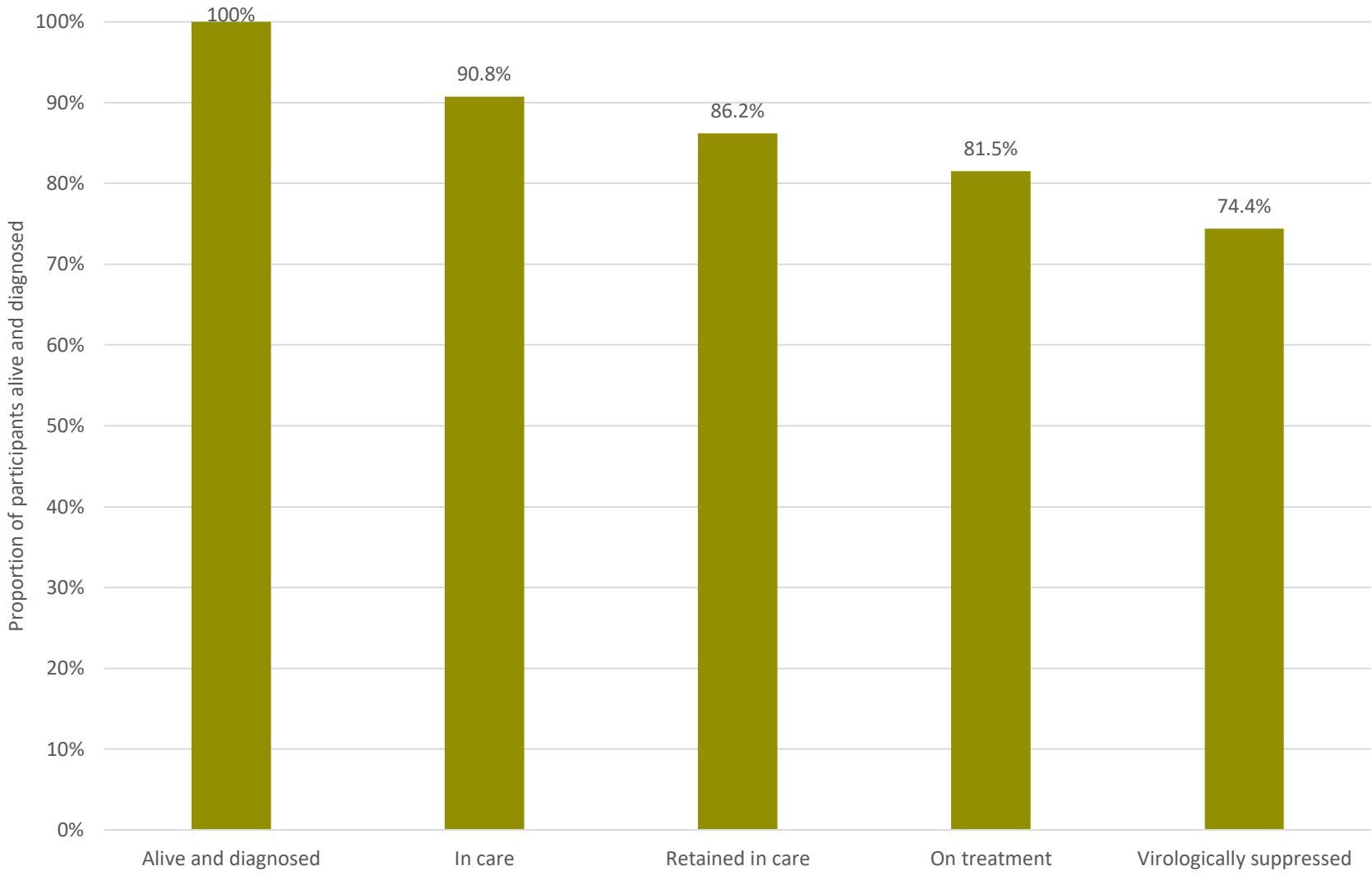

Figure 5.2. HIV care cascade in Manitoba. *N* = 703 at *alive and diagnosed* step.

5.4.1 Examining the cascade through an equity lens

Analyzing the Manitoba cascade data through an equity lens highlights a number of inequalities in the proportion of cohort participants who reach the *in care, retained in care, on treatment,* and *virologically suppressed* steps.

5.4.1.1 Age and sex

The equiplot in Figure 5.3 shows that a greater proportion of participants reach all four cascade steps as their age increases. Our multivariable logistic regression analyses support this (Table 5.2 through Table 5.5), indicating that the odds of a participant meeting the criteria to be included in each cascade step (as per Box 5.1) increases significantly with each year of age. Meanwhile, the equiplot illustrating cascade estimates for male and female participants (Figure 5.4) highlights similarities between groups, with distinguishable differences only in the final cascade step. The multivariable model corroborates this interpretation; AORs in Table 5.2, Table 5.3, and Table 5.4 indicate that participants' sex does not significantly influence whether or not they are *in care, retained in care,* or *on treatment,* respectively, but when controlling for all other equity variables, the odds of female cohort participants reaching the *virologically suppressed* step (Table 5.5) are 65% greater than the odds of the same for males (AOR: 1.65, 95%CI: 1.04-2.61).

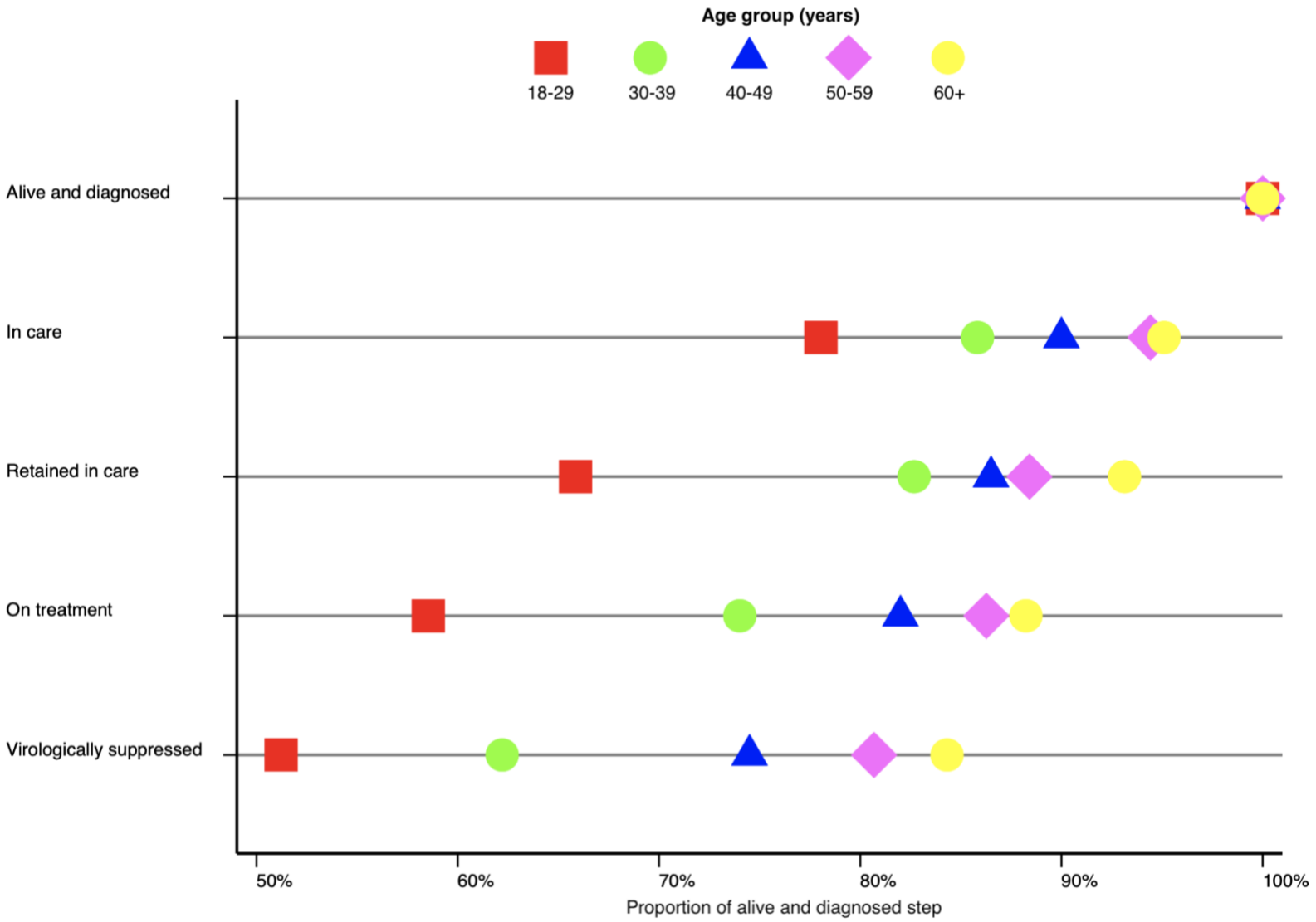

Figure 5.3. Inequalities across the Manitoban HIV care cascade, by age group.

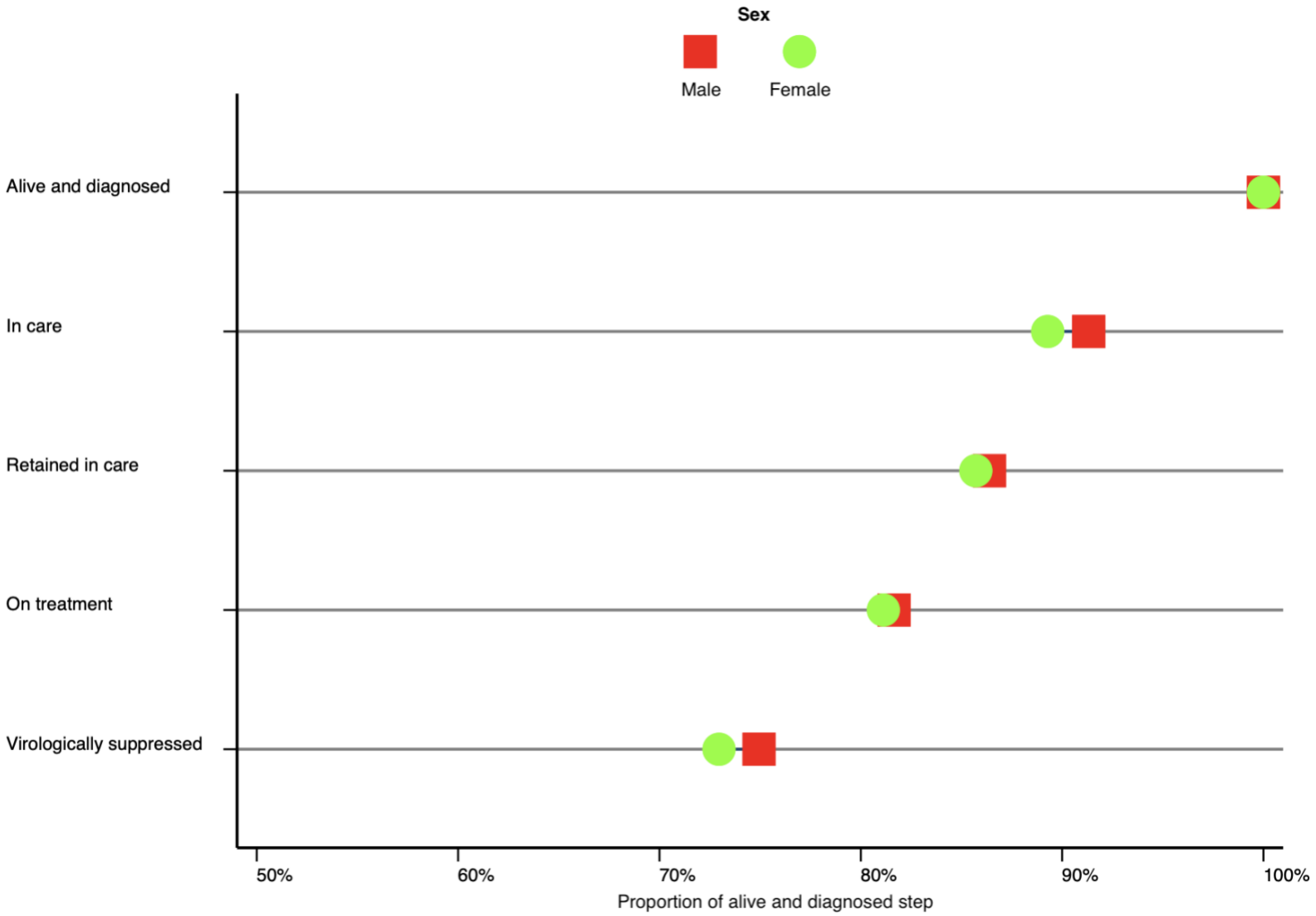

Figure 5.4. Inequalities across the Manitoban HIV care cascade, by sex.

5.4.1.2 Geography

Inequalities are observed between the proportions of cohort participants in each cascade step when the cohort data are disaggregated by geographic regions (Figure 5.5). Given that the large majority (81.9%) of cohort participants reside in the Winnipeg, the proportion of Winnipeg-based cohort participants in each cascade step are similar to the cascade estimates for the entire cohort, depicted in Figure 5.2. Compared to cohort participants living in Winnipeg, those living in eastern Manitoba have significantly greater odds of being *virologically suppressed* (AOR: 3.37, 95%CI: 1.15-9.90; Table 5.5). Meanwhile, Figure 5.5 highlights relatively low proportions of cohort participants living in western Manitoba or living outside of the province in each cascade step, compared to those in other health regions. Logistic regression analyses indicate that, compared to those living in Winnipeg, the odds of being *in care* (Table 5.2) are significantly lower for participants living in western Manitoba (AOR: 0.32, CI95%: 0.12-0.88). Visual interpretation of the equiplot in Figure 5.5 suggests a large discrepancy in the proportion of cohort participants living in southern Manitoba who are *virologically suppressed* (Table 5.5) compared to participants living in other regions of Manitoba, but this difference loses statistical significance in the adjusted model (AOR: 0.50, 95%CI: 0.22-1.16).

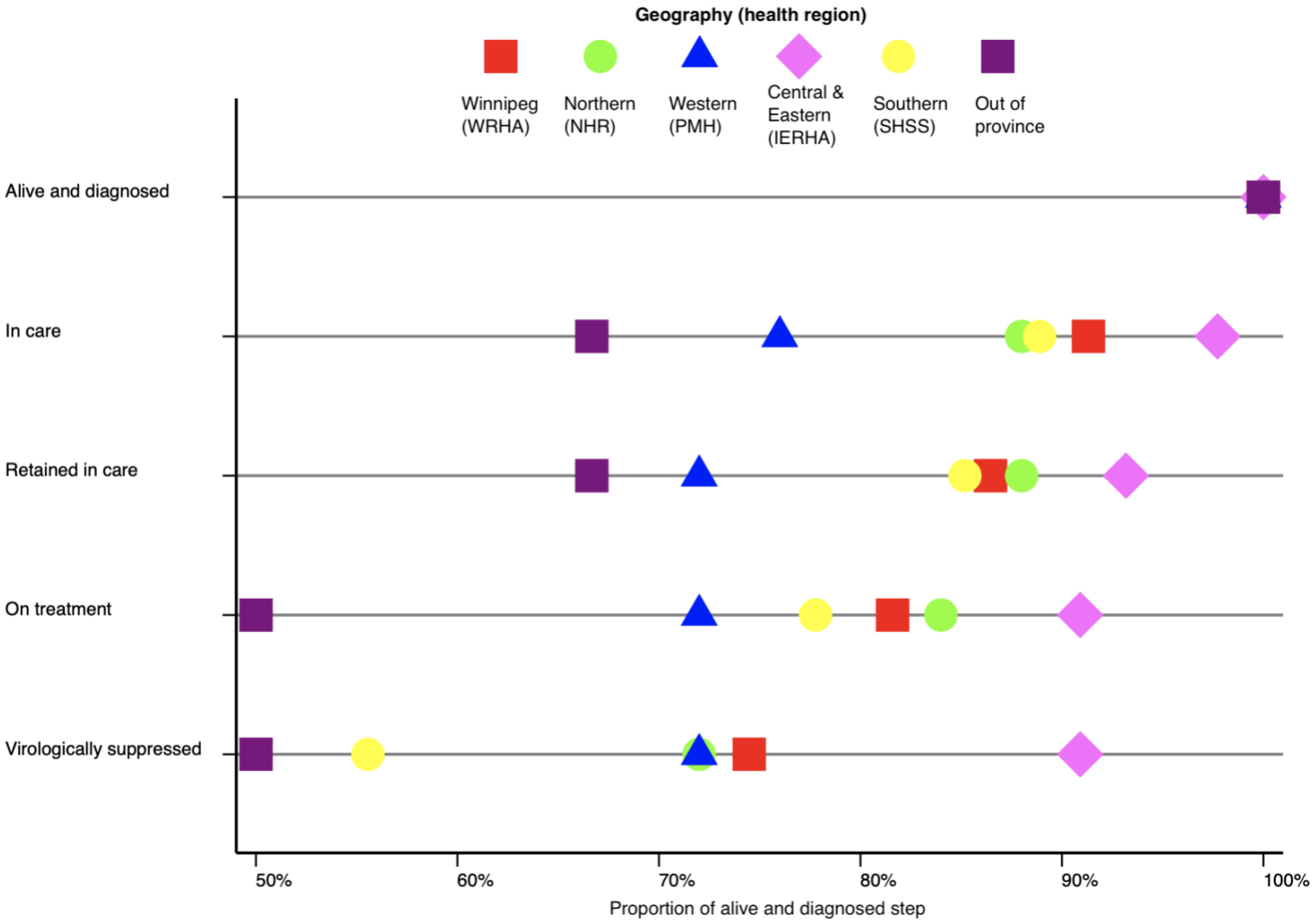

Figure 5.5. Inequalities across the Manitoban HIV care cascade, by geography.

5.4.1.3 Ethnicity

Equiplot data in Figure 5.6 illustrate that white cohort participants represent the group with the greatest proportion in each step across the cascade, relative to participants in other ethnicity categories. The proportions of participants who identify as non-Indigenous people of colour (that is, sub-Saharan African/Caribbean/Black and Other ethnicity categories) are relatively low in the *in care* and *retained in care* steps, whereas the proportions of Indigenous participants in the *on treatment* and *virologically suppressed* steps are relatively low (Figure 5.6); these differences are not significant when controlled for other equity variables. Participants categorized as *on treatment* (Table 5.4) and *virologically suppressed* (Table 5.5) are approximately half as likely to be Indigenous than white (AOR: 0.55, 95%CI: 0.33-0.92 and AOR: 0.54, 95%CI: 0.34-0.84, respectively).

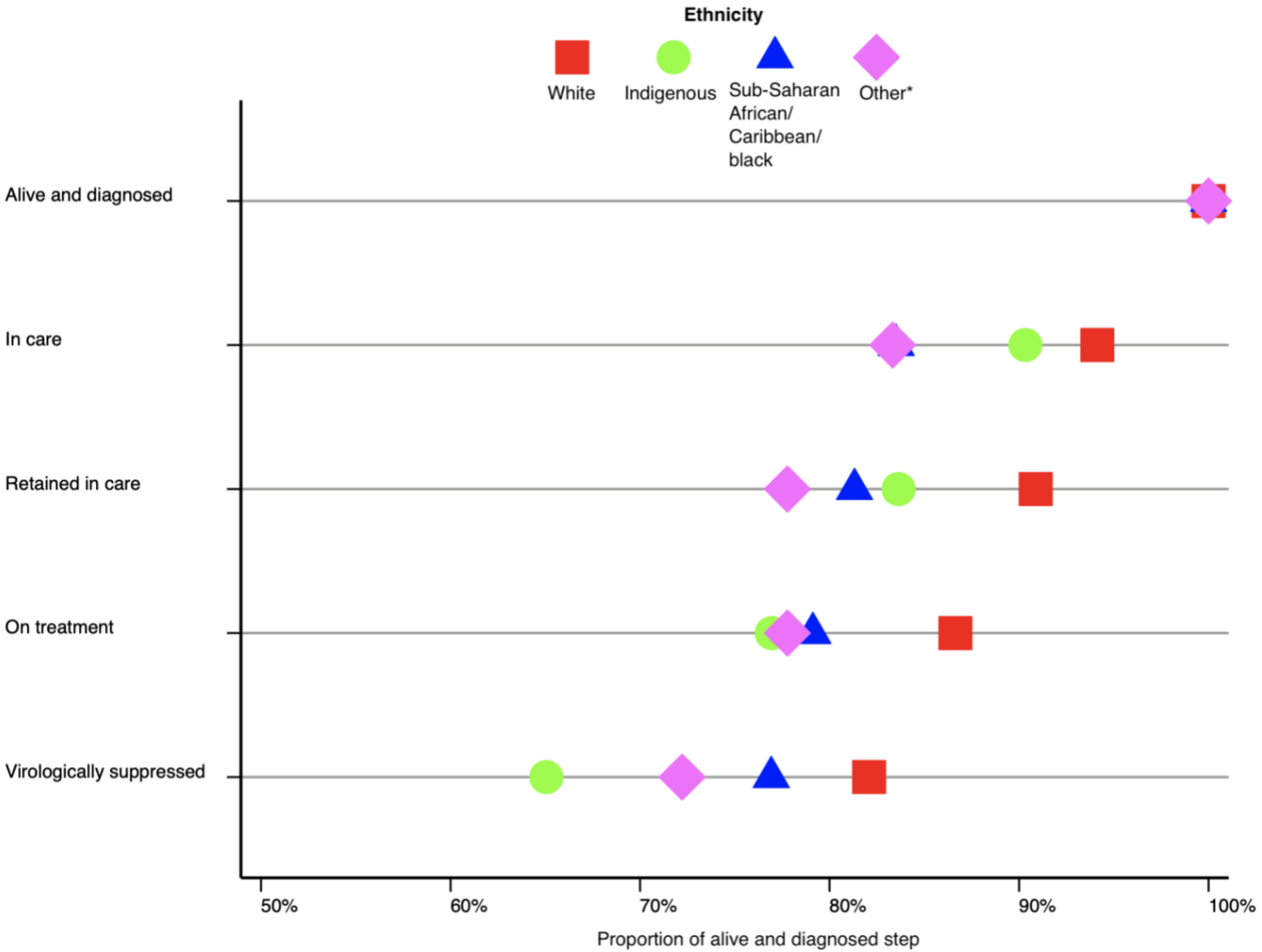

Figure 5.6. Inequalities across the Manitoban HIV care cascade, by ethnicity.

5.4.1.4 Immigration status

After controlling for all other equity variables, a participant's immigration status was not found to influence their odds of being in a given cascade step (Table 5.2 through Table 5.5). However, the equiplot in Figure 5.7 highlights a number of important inequalities between groups and, in general, the proportion of participants who had immigrated to Canada in 2001 or later is notably lower than the proportion of non-immigrant participants in the *in care*, *retained in care,* and *on treatment* cascade steps.

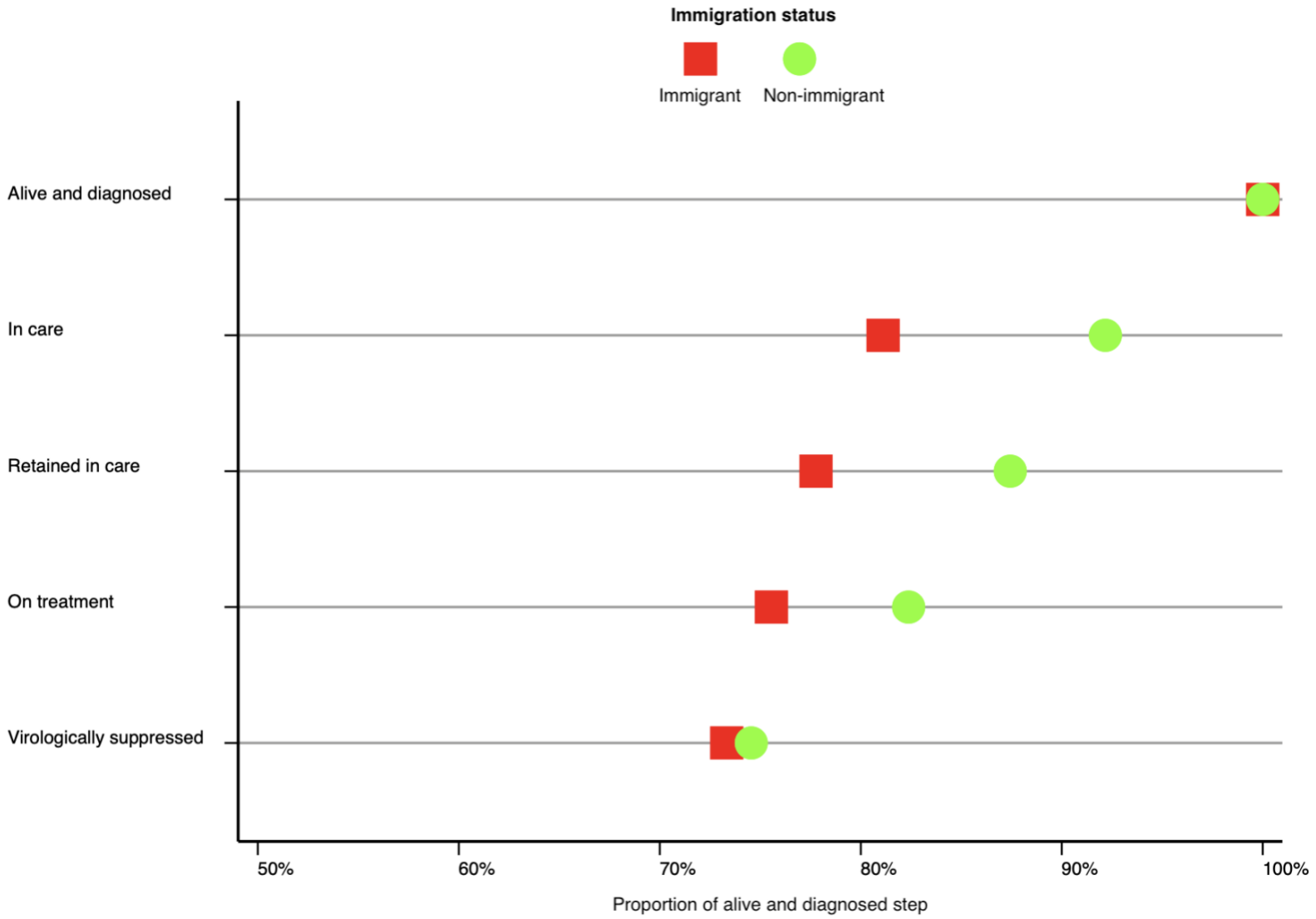

Figure 5.7. Inequalities across the Manitoban HIV care cascade, by immigration status.

5.4.1.5 HIV exposure category

Disaggregating cascade data by HIV exposure category (Figure 5.8) also highlights inequalities across cascade steps, particularly among cohort participants whose primary HIV exposure risk is injection drug use (IDU). Compared to male participants reporting condomless sex with other men (MSM), participants with history of injection drug use are half as likely to be included in the *virologically suppressed* step (Table 5.5, AOR: 0.52, 95%CI: 0.29-0.92). The proportion of participants reporting condomless sex—either MSM or heterosexual—as their primary HIV exposure categories are distributed similarly across cascade steps (Figure 5.8), although a slight inequality emerges between these groups at the *virologically suppressed* stage.

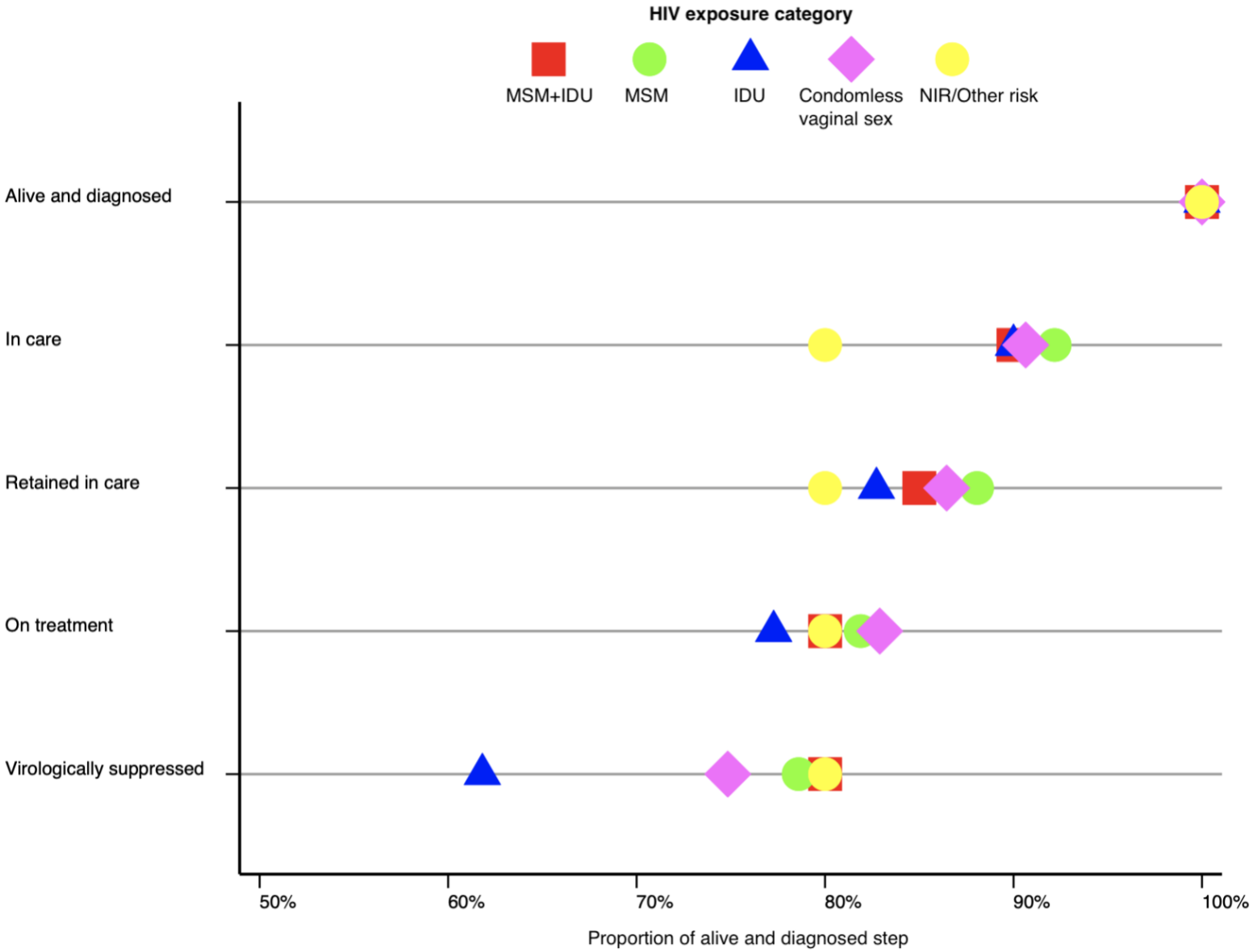

Figure 5.8. Inequalities across the Manitoban HIV care cascade, by HIV exposure category.

Table 5.2. Crude and adjusted odds ratios (AOR) from multivariable logistic regression analysis: Factors associated with reaching the *in care* step of the HIV care cascade among clinical cohort participants.

	In care					
	Crude OR	**95%CI**	***p*-value**	**AOR**	**95%CI**	***p*-value**
Age (years)	1.59	1.26-2.01	0.000*	1.54	1.19-1.98	0.001*
Sex						
Male	*Ref.*			*Ref.*		
Female	0.79	0.46-1.37	0.404	1.25	0.63-2.47	0.518
Geography (by region)						
Winnipeg	*Ref.*			*Ref.*		
Northern Manitoba	0.70	0.20-2.41	0.569	0.80	0.20-3.20	0.750
Western Manitoba	0.30	0.11-0.79	0.015*	0.32	0.12-0.86	0.025*
Eastern Manitoba	4.09	0.55-0.32	0.168	3.02	0.40-2.98	0.286
Southern Manitoba	0.76	0.22-2.61	0.664	0.68	0.18-2.50	0.561
Out of province	0.19	0.03-1.06	0.059	0.17	0.03-1.04	0.055
Ethnicity						
White	*Ref.*			*Ref.*		
Indigenous	0.58	0.31-1.09	0.090	0.75	0.36-1.55	0.433
Sub-Saharan African/Caribbean/Black	0.32	0.15-0.66	0.002*	0.34	0.14-0.82	0.017*
Other	0.31	0.11-0.84	0.022*	0.36	0.13-1.04	0.059
Immigration status						
Non-immigrant	*Ref.*			*Ref.*		
Immigrant	0.36	0.20-0.67	0.001	0.80	0.25-2.58	0.709
Exposure category						
Condomless sex between males (MSM) only	*Ref.*			*Ref.*		
MSM + injection drug use (IDU)	0.76	0.16-3.54	0.730	0.75	0.15-3.67	0.726
IDU only	0.76	0.35-1.66	0.497	0.94	0.37-2.39	0.892
Condomless vaginal (heterosexual) sex	0.82	0.45-1.50	0.525	1.11	0.50-2.45	0.798
No identified risk (NIR)/Other risk	0.34	0.10-1.11	0.075	0.42	0.10-1.69	0.220

* Statistically significant at $p<0.050$

Table 5.3. Crude and adjusted odds ratios (AOR) from multivariable logistic regression analysis: Factors associated with reaching the *retained in care* step of the HIV care cascade among clinical cohort participants.

	Retained in care					
	Crude OR	**95%CI**	***p*-value**	**AOR**	**95%CI**	***p*-value**
Age (years)	1.48	1.22-1.80	0.000*	1.44	1.17-1.78	0.001*
Sex						
Male	*Ref.*			*Ref.*		
Female	0.95	0.59-1.52	0.816	1.54	0.87-2.73	0.138
Geography (by region)						
Winnipeg	*Ref.*			*Ref.*		
Northern Manitoba	1.14	0.34-3.93	0.825	1.40	0.37-5.26	0.618
Western Manitoba	0.40	0.16-0.99	0.049*	0.43	0.17-1.10	0.079
Eastern Manitoba	2.14	0.65-7.08	0.212	1.79	0.53-6.12	0.350
Southern Manitoba	0.90	0.30-2.67	0.850	0.95	0.30-2.98	0.933
Out of province	0.31	0.06-1.74	0.184	0.37	0.06-2.17	0.268
Ethnicity						
White	*Ref.*			*Ref.*		
Indigenous	0.51	0.31-0.85	0.010*	0.60	0.34-1.08	0.088
Sub-Saharan African/Caribbean/Black	0.44	0.23-0.84	0.013*	0.45	0.21-0.96	0.039*
Other	0.35	0.15-0.84	0.019*	0.40	0.16-1.00	0.052
Immigration status						
Non-immigrant	*Ref.*			*Ref.*		
Immigrant	0.50	0.29-0.87	0.015	0.71	0.25-2.03	0.525
Exposure category						
Condomless sex between males (MSM) only	*Ref.*			*Ref.*		
MSM + injection drug use (IDU)	0.77	0.21-2.78	0.688	0.85	0.23-3.21	0.814
IDU only	0.65	0.35-1.21	0.178	0.74	0.36-1.56	0.432
Condomless vaginal (heterosexual) sex	0.86	0.52-1.43	0.574	1.00	0.53-1.90	0.998
No identified risk (NIR)/Other risk	0.54	0.17-1.73	0.302	0.52	0.14-1.90	0.323

* Statistically significant at $p<0.050$

Table 5.4. Crude and adjusted odds ratios (AOR) from multivariable logistic regression analysis: Factors associated with reaching the *on treatment* of the HIV care cascade among clinical cohort participants.

	On treatment					
	Crude OR	**95%CI**	***p*-value**	**AOR**	**95%CI**	***p*-value**
Age (years)	1.50	1.26-1.79	0.000*	1.47	1.22-1.78	0.000*
Sex						
Male	*Ref.*			*Ref.*		
Female	0.97	0.63-1.47	0.870	1.43	0.85-2.41	0.174
Geography (by region)						
Winnipeg	*Ref.*			*Ref.*		
Northern Manitoba	1.18	0.40-3.52	0.761	1.35	0.42-4.30	0.615
Western Manitoba	0.58	0.24-1.42	0.234	0.625	0.25-1.59	0.324
Eastern Manitoba	2.26	0.79-6.44	0.129	2.06	0.70-6.07	0.188
Southern Manitoba	0.79	0.31-2.00	0.619	0.92	0.34-2.48	0.875
Out of province	0.23	0.04-1.13	0.071	0.28	0.05-1.47	0.132
Ethnicity						
White	*Ref.*			*Ref.*		
Indigenous	0.51	0.33-0.79	0.003*	0.56	0.34-0.93	0.026*
Sub-Saharan African/Caribbean/Black	0.58	0.32-1.07	0.081	0.53	0.26-1.07	0.076
Other	0.54	0.23-1.26	0.156	0.67	0.27-1.62	0.369
Immigration status						
Non-immigrant	*Ref.*			*Ref.*		
Immigrant	0.66	0.39-1.12	0.121	0.66	0.24-1.81	0.422
Exposure category						
Condomless sex between males (MSM) only	*Ref.*			*Ref.*		
MSM + injection drug use (IDU)	0.88	0.28-2.77	0.833	1.10	0.34-3.60	0.871
IDU only	0.75	0.4301.31	0.312	1.00	0.52-1.91	0.991
Condomless vaginal (heterosexual) sex	1.07	0.69-1.67	0.757	1.31	0.74-2.31	0.352
No identified risk (NIR)/Other risk	0.88	0.28-2.77	0.833	0.92	0.26-3.23	0.899

* Statistically significant at $p<0.050$

Table 5.5. Crude and adjusted odds ratios (AOR) from multivariable logistic regression analysis: Factors associated with reaching the *virologically suppressed* step of the HIV care cascade among clinical cohort participants.

	Virologically suppressed					
	Crude OR	**95%CI**	***p*-value**	**AOR**	**95%CI**	***p*-value**
Age (years)	1.53	1.31-1.80	0.000*	1.52	1.27-1.81	0.000*
Sex						
Male	*Ref.*			*Ref.*		
Female	0.90	0.62-1.31	0.588	1.65	1.04-2.61	0.034*
Geography (by region)						
Winnipeg	*Ref.*			*Ref.*		
Northern Manitoba	0.88	0.36-2.15	0.781	1.06	0.40-2.80	0.913
Western Manitoba	0.88	0.36-2.15	0.781	1.06	0.41-2.70	0.910
Eastern Manitoba	3.43	1.21-9.74	0.021*	3.37	1.15-9.90	0.027*
Southern Manitoba	0.43	0.20-0.94	0.034*	0.50	0.22-1.16	0.107
Out of province	0.34	0.07-1.72	0.193	0.56	0.10-3.07	0.506
Ethnicity						
White	*Ref.*			*Ref.*		
Indigenous	0.41	0.28-0.60	0.000*	0.54	0.34-0.85	0.007*
Sub-Saharan African/Caribbean/Black	0.73	0.41-1.28	0.273	0.80	0.42-1.52	0.497
Other	0.57	0.26-1.24	0.157	0.69	0.30-1.56	0.372
Immigration status						
Non-immigrant	*Ref.*			*Ref.*		
Immigrant	0.94	0.57-1.55	0.805	0.83	0.33-2.07	0.683
Exposure category						
Condomless sex between males (MSM) only	*Ref.*			*Ref.*		
MSM + injection drug use (IDU)	1.09	0.35-3.40	0.883	1.38	0.42-4.50	0.595
IDU only	0.44	0.27-0.72	0.001*	0.52	0.29-0.92	0.025*
Condomless vaginal (heterosexual) sex	0.81	0.54-1.21	0.301	0.84	0.50-1.39	0.491
No identified risk (NIR)/Other risk	1.09	0.35-3.40	0.883	1.06	0.31-3.63	0.925

* Statistically significant at $p<0.050$

5.5 Discussion

Our analyses highlight important inequalities in the proportions of cohort participants within different sociodemographic groups and HIV risk categories who reach each HIV care cascade step. Notably, disaggregating our cascade data has called attention to clear inequalities in HIV care and outcomes by age, ethnicity, immigration status, and HIV exposure category among cohort participants. Individuals who are younger, non-white, have immigrated to Canada within the past twenty years, and/or identify injection drug use as a primary HIV risk exposure are less likely than their counterparts to reach subsequent cascade steps. These trends are not unprecedented; similar inequalities across the cascade have been noted in a variety of contexts [70, 100, 102, 152, 193]. While our multivariable logistic regression analyses highlight specific inequalities of statistical significance across the cascade, the use of equiplots to analyze disaggregated cascade data is an important method for identifying notable inequalities that, although not statistically significant, are highly relevant and should be seriously taken into consideration during programmatic planning and design to ensure equitable health outcomes across the population. On the quest to generate evidence that can inform policy and program development aimed at minimizing health inequities, using cascade data, both aggregated and disaggregated, to identify inequalities in health outcomes and service access, delivery, and utilization is necessary, though still not sufficient. As Seckinelgin [140] and Zamora and colleagues [139] have argued, employing additional methodologies, such as qualitative inquiry and community-based participatory research, to inform policy and program design is crucial.

When it was first introduced in 2011 by Gardner and colleagues [1], the spectrum of engagement of HIV care, which ultimately became the HIV care cascade, was framed as an analytic tool that is useful for mapping individual- and population-level progression through the

continuum of HIV care services. Specifically, Gardner's model [1] provides a framework through which to determine the proportion of individuals in various stages along the continuum—and to "explore the potential impact of interventions to improve engagement in care" (p.795). However, over time, the cascade, and its further-simplified counterparts the 90-90-90 Initiative [50] and the 95-95-95 Fast-Track targets [175], have been adopted or endorsed by global technical and policy normative bodies (for example, UNAIDS [50, 175] and the WHO [194]), and used to guide and influence international HIV policy development [140]. Expanding the utility of the cascade framework from an analytic tool to a large-scale decision- and policy-making framework is problematic because, as Seckinelgin [140] notes, "the model itself does not analyse the broader socio-political and economic conditions that interact with individuals' experiences of HIV and that inform their decisions to engage with health services" [140]. In the process of developing health policies that align with the principles of health equity and the SDG commitment to leaving no one behind, it is essential for decision-makers to thoroughly consider how social determinants of health influence and manifest inequalities in health outcomes and access to health services [132, 136].

As demonstrated here, performing equity analyses using HIV care cascade data, and illustrating inequalities along the cascade using equiplots, concisely draws attention to points along the cascade at which specific groups of individuals are not optimally engaged in HIV care nor reaching target health outcomes. Still, these analyses provide insufficient context or explanation for observed "gaps" along the cascade. In order to appreciate nuances in observed inequalities across the cascade, and to understand, for example, why people are having a hard time engaging in their HIV care and how to best support equitable access for all, complementary

research approaches, namely qualitative inquiry and community-based participatory research, are necessary [139, 140, 195].

Here, we provide a brief description of one way to maximize the utility of innovative data visualization techniques, such as the equiplot, using our analyses in this paper as an example. In Figure 5.5, obvious discrepancies exist in the proportions of cohort participants from different geographical regions in Manitoba falling within each cascade step. Of particular interest to the Manitoba HIV Program may be the relatively low proportions of individuals living in western Manitoba categorized as *in care* and the substantial leakage at the *virologically suppressed* step among participants living in southern Manitoba. Indeed, previous research has also identified substantial geographic heterogeneity in engagement in HIV care [150, 155], some of which may be attributable to limited access to services due to physical distance [196], or other individual-, community-, and structural-level barriers [155, 197, 198]. Although our disaggregated analyses of the cascade have provided a useful starting point for understanding geographic heterogeneity in HIV care in Manitoba, further mixed methods explorations will be necessary to delve into understanding the complex circumstances that shape inequities along the cascade before meaningful recommendations can be made to inform local programming or policy. A next step to understand geographic inequalities will require further disaggregating data (for example, by sex, age, socioeconomic status) to uncover whether specific groups *within* geographic regions are further vulnerable to suboptimal engagement. Once a reasonable level of granularity is achieved in identifying "key groups" who may require additional support to engage in HIV care, program adjustments and policy development should then be based upon further-contextualized understandings of barriers to engagement in care through meaningful community involvement in program and policy decisions [139, 195]. Policy and programmatic decisions aimed at reducing

health inequities must incorporate nuanced conceptualizations of how the various factors that influence access to and engagement with necessary and appropriate health services interact and overlap [198] to create specific conditions that prevent individuals from progressing through the HIV care cascade and other care continua [140]. If these complexities are not considered, and instead the linear logic inherent to the cascade [3, 140] is privileged, policies intended to reduce gaps in equity will continue to miss the mark.

5.5.1 Study limitations

This study has a few limitations that must be noted. First, a number of limitations inherent to the design of our clinical cohort have been described in detail in Chapter 3 andChapter 4, and in previous work [199]. Opportunities to participate in the cohort are introduced to individuals in the context of their appointments with the Manitoba HIV Program; participation is optional and does not impact the way that HIV care and other services are received. As such, we have to assume that selection bias may be influencing our analyses, and actual engagement in HIV care among the clinic population may be lower than we are able to assess from the cohort. For the same reasons, we cannot presume that our findings are generalizable to the broader population of people living with HIV in Manitoba, although previous work suggests that these data are reasonably representative of larger population in HIV care in Manitoba (Chapter 3). Second, available data were limited such that we were unable to analyse the Manitoban HIV care cascade by income, level of education, or other socioeconomic status (SES) indicators. This will be an important addition to this work, which we will undertake as we move forward with more detailed analyses of our cohort data.

5.6 Conclusion

Overall, our findings highlight a need for further investigation into the complex and dynamics circumstances that shape the lives of people living with HIV in Manitoba and, ultimately, influence the ability of certain groups to engage in their HIV care. While our cascade equity analyses provide a useful starting point to work toward achieving health equity and leaving no one behind for people living with HIV in Manitoba, eliciting meaningful policy and programming change will require deeper, more comprehensive work to understand barriers and facilitators to engagement in care.

Chapter 6. Discussion: Implications, Future Directions, and Conclusions

6.1 Summary, implications, and contributions of presented research

Despite persistently high annual rates of new HIV infection in Manitoba relative to the rest of Canada [17], up to now, very little research has focused on developing a deeper understanding of the factors contributing to the local epidemic, or the clinical epidemiology of HIV in the province. Contributing to this, Manitoba does not currently have a system in place to facilitate the routine collection of clinical data from people living with HIV in the province. While potentially linkable datasets containing relevant HIV-related information do exist in the province [161, 168], a single database housing all relevant datasets has not been available, thus limiting the ability of decision-makers and program implementers to develop evidence-based policies and programming in Manitoba. However, through the work presented in this dissertation, a number of these issues have been addressed; the three studies collectively represent the most comprehensive examination of HIV in the province to date. Furthermore, the data infrastructure and the methods and tools developed throughout this work have laid a foundation upon which to base future HIV-related research questions in Manitoba, with critical policy and programming implications.

First, Chapter 3 details the processes involved in the development of the LHIV-Manitoba clinical cohort, the first comprehensive source of de-identified, individual-level linked health data from people living with HIV and/or receiving HIV care in the province. The findings in Chapter 3 summarize select, preliminary descriptive analyses of clinical data from cohort

participants. Over two-thirds of cohort participants are between 40 and 64 years old and the large majority are male. White and Indigenous participants make up a similar proportion of the total cohort population, but individuals self-identifying as sub-Saharan African/Caribbean/Black are underrepresented. Condomless vaginal sex is the most commonly reported mode of HIV acquisition among both male and female cohort participants. Notably, the majority of cohort participants had entered into care with the Manitoba HIV Program relatively late, with CD4 counts ≤350 cells/mm3, and nearly one-third had been diagnosed with an opportunistic infection within six months of entry into care. Rates of chronic comorbidity are high among cohort participants, with approximately 40% having at least one chronic diagnosis in addition to HIV. Importantly, these findings are similar to the data presented in annual Manitoba HIV Program reports [23, 26, 27]. This suggests that although findings presented in Chapter 3 indicate that the demographic characteristics of cohort participants are different from those of the larger clinic population, their clinical characteristics and outcomes might not be quite as dissimilar.

Prospective cohorts are among the most useful data sources for studying epidemiological trends in HIV. With the establishment of the clinical cohort presented in this dissertation, Manitoba now joins British Columbia [4], Ontario [35, 200], and Newfoundland and Labrador [199] in being one of the few Canadian jurisdictions that have established population-based clinical cohorts of people living with HIV in the province. Previous work has highlighted the benefits of using longitudinal data from prospective cohorts to develop HIV care cascade models, as they are able to better capture the complexities inherent to the cyclical process of engagement in care for people living with chronic conditions, including HIV [45, 46]. As such, it is anticipated that as the LHIV-Manitoba clinical cohort matures and subsequent years of data are added to the database, a more nuanced understanding of long-term trends in HIV care, as

well as a clearer idea of which groups are being left behind, will be within reach. Additionally, with the inclusion of comprehensive comorbidity data, the clinical cohort presents opportunities to explore policy- and program-relevant questions pertaining to resource allocation and clinical management and care for people living with multiple chronic conditions [201, 202] in the province. This is expected to be particularly germane as research around aging with HIV is an increasingly relevant field [203], but has not yet been extensively explored in Manitoba. Finally, in line with Program Science principles, the clinical cohort has been strategically established as an embedded component within the larger operations of the Manitoba HIV Program. This means that data from the cohort can be readily accessed to inform programmatically relevant research questions in a timely and efficient manner.

Next, using the individual-level data housed within the clinical cohort database, Chapter 4 expounds the methods and processes involved in deriving locally relevant indicator definitions for each step of an HIV care cascade, and presents the first-ever set of cascade estimates for Manitoba. In testing the sensitivity of each indicator definition, wide variation in the estimates for each cascade step are evident, depending upon the data included in the definition and the stringency of the definitions' parameters. Upon choosing a set of preferred indicator definitions, a final Manitoba cascade is presented, which encouragingly highlights that 81.5% of cohort participants who were alive and diagnosed with HIV in 2017 were retained in care, and 74.4% were virologically suppressed—thus meeting the 90-90-90 targets set by UNAIDS in 2014 [50], though slightly missing the more optimistic 95-95-95 Fast-Track targets introduced the following year [51]. Arguably more importantly, the analyses in Chapter 4 draw attention to two important points of leakage in the Manitoban cascade. First, over 9% of cohort participants are not categorized as *in care*, meaning that these individuals did not have any clinical contact with the

Manitoba HIV Program within the first 6 months of the 2017 calendar year. Such an outstanding drop-off in engagement at such an early point in the continuum of HIV care is particularly concerning and warrants further investigation. A second notable point of leakage occurs at the *virologically suppressed* step, at which point 7% of the participants who were categorized as *on treatment* did not have evidence of a suppressed viral load (<200 HIV RNA copies/mL) at their last test of the year. Although, overall, a promising proportion of cohort participants who were on treatment were also virologically suppressed, understanding the circumstances around the 7% of participants who did not reach virologic suppression, despite being prescribed ART, is of critical programmatic and public health importance.

A primary intention of the study presented in Chapter 4 was to develop an intuitive and adaptable HIV care cascade framework that is readily available for use by the Manitoba HIV Program as a way to monitor program performance. The indicator definitions were intentionally developed to be flexible enough to accommodate the use of basic clinical data that can be quickly procured and analyzed within a clinical setting. Importantly, this cascade framework could be conceptualized as a "micromonitoring" tool [149] for use by the Manitoba HIV Program to establish an understanding of the needs of clients, and to determine whether or not they are being met through program services and activities. Micromonitoring is one strategy within the larger notion of microplanning—a core component of a Program Science approach [149, 204]—that has been implemented in a variety of global contexts [149, 204, 205] to engage frontline providers in the active management of service provision to accommodate local need. Specifically, in the context of the Manitoba HIV Program, the cascade framework developed through the work presented in Chapter 4 can be used to identify leakages and bottlenecks in the continuum of care services being provided, which can then be used as "jumping off" points upon

which to base operational adjustments, adding valuable nimbleness to programming and clinical practice.

Furthermore, the cascade analyses in Chapter 4 represent an important contribution to the larger body of literature describing HIV epidemiology across Canada, and more specifically, in the Prairie provinces. As this dissertation presents the first set of full HIV care cascade estimates for Manitoba, these results provide some much-needed depth to our understanding of the clinical epidemiology of HIV at a provincial level. While previous work by PHAC has generated national 90-90-90 indicator estimates [53], analyses specific to Manitoba have not been publicly available. Recently, MHSAL and PHAC have again been working together using provincial HIV data from 2018 to develop updated 90-90-90 estimates. Preliminary estimates developed by the joint provincial-federal initiative using 2018 data, indicate that 83.3% of all people living with HIV in Manitoba have been diagnosed, 83.0% of those diagnosed with HIV are on treatment, and 87.2% of those on treatment are virologically suppressed (personal communication, J. Paul, 16 April 2020). While the cascade presented in Chapter 4 does not include an estimate for the diagnosed fraction, the *on treatment* cascade estimate of 81.5% is similar to that derived by MHSAL and PHAC, and the *virologically suppressed* estimate from the cascade model is more divergent, at 74.4%. It is important to note that some of this discrepancy is likely due to a difference in indicator definitions employed to derive estimates. However, this comparison does highlight the potential utility of the Manitoba HIV care cascade model and the clinical cohort to act as reasonable proxies for estimating provincial-level trends in the clinical epidemiology of HIV. Further work should focus on understanding the generalizability of analyses from the clinical cohort to the larger population of people living with HIV in Manitoba.

Although a locally contextualized HIV care cascade can be a useful tool for the microplanning of program activities, the temptation to directly derive inspiration for policy change from aggregate, population-level cascade estimates is best avoided. Seckinelgin [140], as well as Zamora and colleagues [139], emphasize the imprudence of basing high-level policy decisions on cascade data without first attempting to understand the factors shaping the observed trends in the continuum of HIV care. Indeed, Seckinelgin [140] notes a key limitation to translating the linear logic of a conventional cascade framework into policy: "… this framing does not produce the knowledge needed to understand social worlds, practices and peoples' lives. … [it] does not allow for thinking about contextualised sustainable wellbeing" (p. 10). Following this logic, with a specific focus on the principles of health equity, the analyses presented in Chapter 5 demonstrate that by disaggregating clinical cohort data by key sociodemographic variables before conducting cascade analyses, important inequalities among subgroups emerge across the entirety of cascade. Specifically, people living with HIV and receiving care in Manitoba who are relatively young, non-white, have immigrated to Canada since 2001, or have a history of injection drug use are less likely engaged in care, or experiencing worse HIV-related outcomes than their counterparts. While these findings are not dissimilar to inequalities that have been identified in different contexts [70, 100, 152, 153], this is the first empirical evidence indicating that such inequalities exist in Manitoba, thus validating "anecdotal" knowledge, rooted in extensive clinical and programmatic experience, that providers and management within the Manitoba HIV Program have held for years.

Before expanding upon the discussion of the potential programmatic and policy implications of these data highlighting inequalities in HIV care coverage in Manitoba, it is worth noting the significance of the innovative adaptation of data visualization techniques presented in

Chapter 5. Equiplots are easily interpretable graphs that illustrate "both the level of coverage in each group and the distance between groups, which represents absolute inequality" [192]. Developed by the International Centre for Equity in Health in Pelotas, Brazil, equiplots have been adopted by Countdown to 2030—a multidisciplinary, international collaborative focused on strengthening countries' capacity to generate meaningful evidence and to enhance monitoring, evaluation, and programming aimed at women's, adolescent's, and children's health—as a key data visualization tool for country equity profiles [206]. However, beyond Countdown to 2030, equiplots have not commonly been used for presenting health equity data, despite their great potential to help disentangle the overlapping and intersecting factors that contribute to inequalities in health and health service coverage. In Chapter 5, equiplots are presented alongside more conventional multiple logistic regression analyses examining the associations between key equity variables and cascade steps. Using both methods, the reader benefits from being able to visually interpret the absolute inequalities across each cascade step and examine the statistical significance of these differences between groups. While statistical significance is one strategy for assessing "differences" between groups, it has the tendency to lead readers' attention away from important differences that, although not statistically significant, have critical implications for program or practice [207]. Along these lines, the equiplot analyses in Chapter 5 draw the eye toward some noteworthy inequalities across the cascade that are not found to be significant in the adjusted logistic regression models. For instance, the equiplot in Figure 5.6 clearly illustrates that the proportion of cohort participants who do not self-identify as white in each cascade step, from *in care* to *virologically suppressed,* is consistently lower than the proportion of white participants in the same steps. However, when we examine the corresponding AORs in Table 5.2 through Table 5.5, only a select few are marked as statistically significantly different from the "white"

ethnicity category. In this case, visualization and interpretation of cascade data through equiplots may be more programmatically useful than examining logistic regression analyses for identifying points of potential intervention and program adjustment.

While basing policy and program decisions on good programmatic and scientific evidence is essential, incorporating and translating that evidence into effective and transformative change involves a complex, multi-phase process [143, 148]. Using hypothetical examples inspired by the equity analysis data presented in Chapter 5, the following steps represent a potential process through which evidence (generated through research using program data) could be incorporated into practice to address inequities in HIV care in Manitoba. It is important to note that while the analyses presented in Chapter 5 provide a starting point for future programmatic and policy work by identifying numerous potential points of intervention to improve service coverage within the Manitoba HIV Program, plenty of follow-up is necessary before transformative change can occur.

Following the identification of inequalities across the cascade as potential points of programmatic and/or policy intervention—for example, Figure 5.7 highlights a substantial discrepancy [inequality] in the proportion of immigrant cohort participants in the *in care*, *retained in care*, and *on treatment* steps—it is necessary to conduct additional investigation to achieve more granularity in our understanding of who, what, and where this inequality is affecting most. Expanding upon the earlier example, if the data were to be further disaggregated by age group, we may (hypothetically) find that the younger, female immigrants are the least likely to be engaged in care. Furthermore, it is also essential to understand the demand- and supply-side barriers that exist to optimal service coverage [137, 139, 140] among key affected groups. Ideally, this information—which adds much-needed nuance to our conceptualization of

the inequality in question—is derived from a combination of programmatic knowledge and in-depth scientific inquiry through collaborative research processes with key informants, including service providers and members of the program's target population [131, 139, 140, 143]. These knowledge-gathering steps are a key part of strategic planning, the first phase in a Program Science approach [142, 143, 149]. Next, the information gathered through strategic planning is used to develop contextualized interventions and service delivery strategies for the program. Importantly, the development of interventions must be enabled by supportive policies that create environments conducive to change [131, 139]. Intersectoral co-operation and multilateral commitments to resource (re-)allocations that facilitate action toward reducing health inequity are imperative [132, 139, 208] to this process. An example of intersectoral collaboration relating to our hypothetical example might involve coordinated planning between MHSAL and local settlement services organizations to provide support systems for newcomers to navigate the Manitoban health system to access HIV care. The final phase of the Program Science process involves the management, monitoring, and evaluation of program outputs and outcomes of the components interventions, partnered with responsive adaptation as needed [142, 143]. In order to ensure that the interests of various stakeholders are being considered, the monitoring and evaluation of program data should be a collaborative process among all levels of stakeholders—those providing and using services, as well as program implementers and funders [143, 149]. A successful operationalization of the Program Science framework inherently requires that the aforementioned steps are carried out in an iterative manner. As such, the monitoring data analyzed and evaluated in the final phase should be used to inform further strategic planning and instigate another "round" of the three-phase process.

6.2 Limitations to presented work

There are numerous limitations to the individual studies presented in this dissertation; these have been acknowledged and largely explicated in Chapter 3 through Chapter 5. Broadly, the primary limitations to this work are related to two key issues: cohort design and data availability.

As with most observational studies, the potential lack of representativeness and generalizability of the clinical cohort to the larger population of people living with HIV in Manitoba are important considerations for the research presented herein. Based on analyses presented in Chapter 3, it is clear that the demographic composition of cohort participants differs from that of larger Manitoba HIV Program client population. At the programmatic level, then, there is a real possibility that the implications of the findings in this dissertation cannot be reliably extrapolated to all clients of the Manitoba HIV Program. Furthermore, due to the clinic-based enrolment procedures described in Chapter 3, cohort participants are more likely to be individuals who attend appointments with the Manitoba HIV Program. This enrolment methodology and the opt-in nature of this cohort, constitute potential sources of selection biases, and as a result, estimates of engagement across the HIV care cascade may overstated in Chapter 4 and Chapter 5. An important strategy for ensuring that our interpretations of these analyses are reasonable has been, and will continue to be, the active engagement of service providers and people with lived experience in dissemination and knowledge translation activities as a form of "member checking" and validation.

The other broad limitation to the presented studies is the unavailability of certain kinds of data that would have been helpful in providing more detailed or nuanced analyses. The HIV care cascade model developed in Chapter 4 was limited by its exclusion of an estimate for the

"undiagnosed fraction" for Manitoba. This indicator, which represents the proportion of people living with HIV who have not been diagnosed and are therefore aware of their status, is the conventional first step in cascade models [1, 4]. The undiagnosed fraction provides critical insight into gaps in HIV testing and the potential "transmission risk" associated with not being aware of one's HIV status. Historically, PHAC has generated estimates for the number of people living with HIV in each jurisdiction using a number of complex methods including a workbook method, two statistical modelling methods, and an iterative spreadsheet model [125] . However, up-to-date analyses estimating the undiagnosed fraction for Manitoba have not been made publicly available and the data within the clinical cohort do not lend themselves to calculating an estimate for this indicator. Despite this, the cascade model in this dissertation presents highly relevant clinical and programmatic information that provides insight into the more "downstream" stages of the continuum of HIV care. Furthermore, datasets contained within the cohort database—the provincial administrative health datasets (Table C. 2 in Appendix C) and the clinical data abstracted from medical records (Table C. 1 in Appendix C)—lack specific information about participants' socioeconomic status, such as employment, individual- or household income, highest completed level of education, or other related indices. This limitation was particularly detrimental to the equity analyses presented in Chapter 5, as income is a well-established predictor of poorer health outcomes generally [127], and suboptimal engagement in HIV care, specifically [100, 151, 209]. While it may be possible in the future to link area-level income quintile data [210] or the socioeconomic factor index (SEFI-2) data [211] to this clinical cohort, at the time that this work was conducted, these variables had not yet been linked to the cohort database.

6.3 Future directions: Recommendations and considerations for moving forward

The presented work provides a foundation upon which to build a larger, more comprehensive platform of clinical epidemiological research on HIV in Manitoba. However, a number of considerations remain to ensure the momentum of this research agenda continues to move forward.

6.3.1 Cohort maintenance and sustainability

As previously described, the establishment of the clinical cohort was funded by the LHIV study, a CIHR-funded program of research. While the LHIV study presented an unprecedented opportunity to expand the scope of HIV research for Manitoba, without the additional support from non-grant-based funds, the sustainability of the clinical cohort is uncertain [199]. Fortunately, as the cohort is embedded within the Manitoba HIV Program, there may be opportunities to seek investments from stakeholders to support the maintenance of this invaluable data source. Moving forward, advocating to potential investors for the support of the clinical cohort will be an important role at the management level of the Manitoba HIV Program.

Since 2018, active recruitment of new participants into the cohort has slowed down as the limited resources supporting enrolment efforts had to be re-focused toward data collection and analysis. However, once the enrolment process is re-prioritized, efforts should focus on supporting the enrolment of participants who are currently under-represented in the cohort (see Table 3.1 in Chapter 3). Additionally, to better integrate the cohort into the operations of the Manitoba HIV Program, it may be useful to consider introducing the idea of research participation to new clients of the Manitoba HIV Program as a part of the clinical intake procedure.

6.3.2 Supplemental data

To enhance the analytic potential of the clinical cohort, it will be necessary to link supplemental datasets to the existing cohort database. In particular, the addition of variables that can contribute to our understanding of cohort participants' socioeconomic status would be useful for better understanding issues of inequity in health service coverage among people living with HIV in Manitoba. The Manitoba Centre for Health Policy (MCHP), housed in the Department of Community Health Sciences, University of Manitoba is one potential source of supplemental datasets; it is highly recommended that linking the cohort database to relevant MCHP datasets is pursued in the future.

Another possibility to supplement the current clinical cohort database is the implementation of a survey among cohort participants. This strategy has been used in other, similar cohorts [35, 212] and can be useful to collect data on facets of participants' lives that are not readily ascertainable through passive data collection from provincial administrative health datasets or medical records.

6.3.3 Remaining research questions and recommended next steps

Using clinical cohort data, the studies comprising Chapter 3 through Chapter 5 present some of the most comprehensive analyses of HIV in Manitoba to date. These pieces of work have established a basis of knowledge upon which to develop new research, building off of findings in this dissertation, or exploring entirely new areas of inquiry.

In order for the findings presented in dissertation to be effectively incorporated into programming, or used to inform policy, it is critical that future research employs qualitative methodologies to explore the reasons behind the inequalities across the HIV care cascade

observed in Chapter 5. Importantly, these inquiries should be directed both at service providers and users of health services—that is, members of the Manitoba HIV Program's target population, as per Tanahashi [137]—in order to develop an understanding of supply- and demand-side barriers to engagement in care. Furthermore, interviews with policymakers and other decision-makers with some control over provincial resource allocation may be useful to develop strategies for effectively incorporating evidence generated through the work in this dissertation, as well as findings from subsequent research, into policy and practice.

Another set of analyses that will be helpful in providing nuance to the findings in this dissertation is the further disaggregation of the data presented in the equity analyses. In order to develop interventions tailored specifically to individuals experiencing the greatest inequalities, it will be necessary to understand, for instance, whether the individuals living in southern Manitoba who have not reached virologic suppression (Figure 5.5) are more likely to be a certain age or sex, or to have a history of injection drug use. Without having to collect additional data, by simply disentangling these factors through further data disaggregation will be able to add substantial programmatically relevant insight to the current findings.

Of course, aside from analyses based on the presented cascade model, there are several different directions in which future research using the clinical cohort data can proceed. For instance, developing an understanding of mortality among people in care with the Manitoba HIV Program has been noted as an area of interest, along with developing a better understanding of care patterns and service utilisation among clients living with multiple comorbidities. The clinical cohort contributes to the already rich data environment in Manitoba; involving stakeholders, and particularly people with lived experience of HIV, in conversations about future directions of HIV research in Manitoba is of central importance. Community programming based

out of Nine Circles Community Health Centre is one avenue through which such engagements might occur.

6.3.4 Dissemination, knowledge translation, and stakeholder engagement

Sharing the knowledge and evidence generated through this work is a critical next step. Three key groups of stake holders are of particular importance: service users/people living with HIV in Manitoba, service providers and program managers/implementers, and decision-makers involved in provincial policy sphere. As previously mentioned, meaningfully engaging people with lived experience in the research process is an essential component to ensuring the implementation of good programs and effective policy. Specifically, in the context of a Program Science framework, community engagement has been highlighted as a key aspect of all three phases—strategic planning, program implementation, and monitoring and evaluation [142, 143, 149]. While a process through which to engage community members in HIV research has not been formally established in the province, certain clinical sites of the Manitoba HIV Program host regular community programming, which could be useful entry points to introduce opportunities for research participation and engagement.

Open discussions about the implications and potential programmatic utility of these research findings between researchers and Manitoba HIV Program managers and implementers (many of whom are also service providers) will facilitate the effective incorporation of the evidence generated into ongoing clinical practice, while providing opportunities for programmers to contribute to the research agenda moving forward. Furthermore, working together, researchers, providers, and program implementers are more likely to develop effective strategies for advocacy directed toward policy change and resource allocation.

Finally, engagement with decision- and policymakers is crucial in order to garner support and buy-in for programmatic adjustments or changes that typically require an input of resources from funding bodies (governmental or otherwise). Effective engagement in this arena requires that researchers and program implementers are able to translate the scientific and programmatic knowledge into language that is palatable to policymakers and aligns with their overarching interests.

6.4 Conclusions

Taken together, the studies in this dissertation provide novel insights into the clinical epidemiology of HIV in Manitoba, thus contributing to the limited body of literature focusing on HIV in the Canadian Prairies. The findings demonstrate that the LHIV-Manitoba clinical cohort is a valuable source of data upon which to base future research that aims to better understand the health and healthcare of people living with HIV in the province. Furthermore, the HIV care cascade model developed contributes a useful tool that can be used to monitor and evaluate the performance of policies and programming aimed at supporting people living with HIV. Importantly, this dissertation has focused on the notion of health equity in the context of HIV care in Manitoba and has centred the importance of maintaining programmatic relevance throughout the research process. In this way, the findings presented contribute to the growing body of literature expressing skepticism toward the uncritical use of the HIV care cascade and the 90-90-90 targets as service delivery end goals [64] or to inform health system policies [140]. Specifically, the findings and subsequent discussions within this dissertation suggest that applying an equity lens to cascade analyses forces research and practice to continue asking why inequalities persist across the cascade and how programs and policies must change to minimize, and ultimately, eliminate them.

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Appendix A. Supplementary materials for Chapter 1

Table A.1. Proposed indicator definitions for a Canadian HIV care cascade, as conceptualized by the Public Health Agency of Canada's National HIV Cascade Working Group.

	PRIMARY INDICATOR			**SUPPLEMENTARY INDICATORS**		
	Numerator	**Denominator (refined)**	**Denominator (crude)**	**Numerator**	**Denominator (refined)**	**Denominator (crude)**
*HIV infected**	Estimated number of people living with HIV (undiagnosed and diagnosed)			Estimated number of people living with HIV (undiagnosed and diagnosed)		
HIV diagnosed†	Number of people diagnosed with HIV in a 12-month period	Estimated number of people living with HIV	-	-	-	-
Linked to care	Number of people with ≥1 HIV clinic visit or ≥1 viral load test in a 12-month period	Number of people diagnosed with HIV	Estimated number of people living with HIV	Number of people with ≥1 HIV clinic visit or ≥1 viral load test within [1, 3, 6, 12] months after HIV diagnosis	Number of people diagnosed with HIV	Number of people diagnosed with HIV
Retained in care	Number of people with ≥2 HIV clinic visits or ≥2 viral load tests	Number of people linked to care (with ≥1 HIV clinic visit or ≥1 viral load	Estimated number of people living with HIV	Number of people with ≥2 HIV clinic visits at least 3 months apart or ≥2 viral	Number of people linked to care (with ≥1 HIV clinic visit or ≥1 viral load	Number of people diagnosed with HIV

	in a 12-month period	test in a 12-month period)		load tests at least 3 months apart in a 12-month period	test in a 12-month period)	
On treatment	Number of people with ≥1 indication of antiretroviral treatment‡ in a 12-month period	Number of people retained in care (≥2 HIV clinic visits or ≥2 viral load tests)	Estimated number of people living with HIV	Number of people with ≥1 indication of antiretroviral treatment in a 12-month period	Number of people linked to HIV care (≥1 HIV clinic visit or ≥1 viral load test)	Number of people diagnosed with HIV
Virologically suppressed	Number of people with a viral load <200 copies/mL at most recent viral load test in a 12-month period	Number of people on treatment (≥1 indication of antiretroviral treatment)	Estimated number of people living with HIV	Number of people with a viral load <200 copies/mL at most recent viral load test in a 12-month period	Number of people linked to HIV care (≥1 HIV clinic visit or ≥1 viral load test)	Estimated number of people diagnosed with HIV

⁎ Every three years, PHAC produces estimates for incident HIV infections in Canada based on modelling exercises that are outlined elsewhere [19].

† PHAC produces annual estimates of new HIV diagnoses in Canada based on routing HIV case reporting by provinces and territories.

‡ Indication of treatment includes evidence of prescribed ART, dispensed ART, or treatment recorded at HIV care encounter (that is, viral load test, clinic visit).

Appendix B. Supplementary materials for Chapter 2

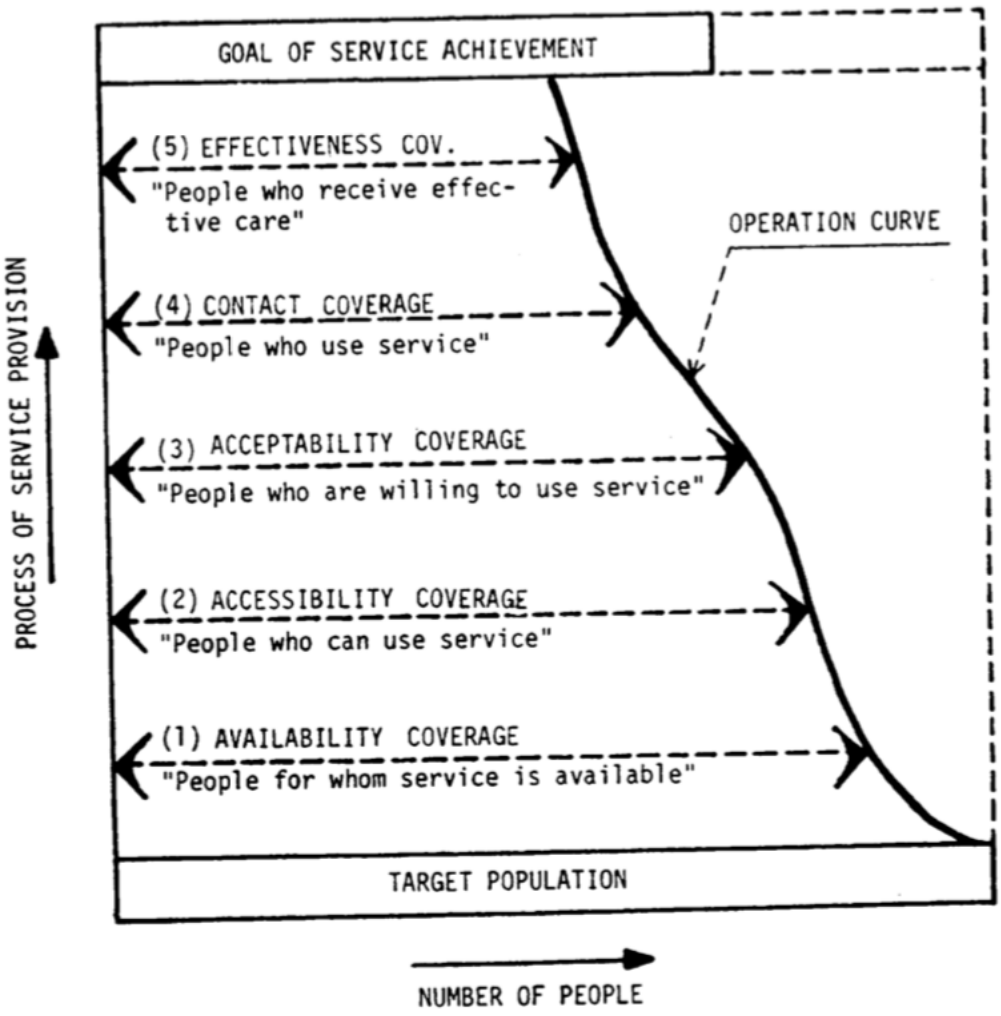

Figure B.1. Five dimensions of coverage in relation to service provision, as depicted in Tanahashi's model of health service coverage [137].

Table B.1. Informed consent form for participation int he LHIV-Manitoba clinical cohort study, English version.

RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM

Title: HIV Clinic Program Database

You are being asked to take part in a research database because you go to the HIV Program Clinic, either at Health Sciences Centre or Nine Circles Community Health Centre. As part of your care, we keep a record of your visits to the clinic. We are asking for consent to use your health information for research and to improve the quality of care.

Purpose

The purpose of this project is to gather information about people with HIV and related conditions. This information will be stored in a database. We want to learn about your signs and symptoms of HIV, your medical history, the impact of the disease, other health conditions and treatments. This information will help researchers learn more about HIV, including treatment and care.

You are being asked for permission to:

- Collect, store and use your health information contained in clinic/hospital records for research into HIV and related conditions.
- Use your health information contained in administrative health databases for research into HIV and related conditions.
- Review your health information from the HIV Clinics to determine if you are eligible to participate in future research studies about HIV and willing to be contacted about future research studies related to HIV.

Procedures

If you agree, information routinely collected whenever you receive care through the HIV Clinic may be used for research. Participating in this database project will not change your normal clinic visit. Information collected for this database will be kept for as long as the HIV Program exists. The database will include the following information:

- A number that replaces your name, to protect your confidentiality
- Information from medical history and physical examinations
- Information from tests and procedures you have, such as blood tests and x-rays

For research purposes, information in this database may be linked with information from your hospital/clinic chart or with information that is collected by Manitoba Health (administrative data).

This can include information on such things as hospitalizations, physician visits and prescriptions. This information is already collected as part of routine service delivery and does not require your consent. However, consent is needed if potentially identifying information for research purposes from these administrative databases will be used.

The University of Manitoba Health Research Ethics Board has approved this database. The University of Manitoba Health Research Ethics Board must approve future research that uses this database. Research that uses information from administrative databases must also be approved by Manitoba Health's Health Information Privacy Committee.

You will not be contacted or notified about future uses of your information. If you tell us that you are interested in participating in future research studies, research staff may review your medical information to see if you are a fit for the study goals. If you are, you may be contacted and asked to participate in these studies. You can decide then if you would like to participate. You do not have to participate in these studies. Each study will require that you give separate consent.

Risks and Benefits

There are no health-related risks to you by participating in this research database. There is, however, the potential risk of loss of confidentiality. Every possible effort will be made to keep your information confidential. Research studies that use your information may not benefit you directly. However, this research may help to provide a better understanding of HIV and related conditions and may improve future care. We hope that this research will benefit HIV positive persons in Manitoba in the future. The Manitoba HIV Program hopes to use information learned from this study to strengthen HIV prevention and care in Manitoba.

Confidentiality

All personal information collected for this study will be kept strictly confidential in accordance with the Personal Health Information Act of Manitoba. Your information will be accessible by the research staff who have been approved to do so. The University of Manitoba Health Research Ethics Board may review database records for quality assurance purposes.

Your name and other personal information that may identify you will not be used or revealed in any papers or presentations about this research. The research data will be stored on password-protected computers in a locked, secure area of the University of Manitoba. Paper records will also be kept in the locked secure area and only the investigators and their research staff will have access to these records. Your name and other information that may identify you will be removed from the data before it is analyzed. We will make every effort to keep your personal information confidential, but we cannot guarantee absolute confidentiality.

Voluntary Participation/Withdrawal from the Study

Your decision to take part in this research database is voluntary and will not affect your personal medical care in any way, even if you decline to participate in this database. No compensation is provided for participation. You may refuse to participate or withdraw from the database at any time. If you decide to withdraw, please contact the HIV Program at 204-xxx-xxxx. If you decide to withdraw, your data will not be available for future use. If you had already agreed to participate and then changed your mind later, your data may already have been used and reported on.

Questions

If you have questions about this database, contact the HIV Program team at 204-xxx-xxxx. For questions about your rights as a research participant, contact The University of Manitoba, Bannatyne Campus Health Research Ethics Board Office at (204) xxx-xxxx.

Statement of Consent

I have read and understood this consent form. By signing this form I give permission for my personal health information to be used for the purpose of research. I was given an explanation about the purpose of using the data collected for this database. I was given enough time and opportunity to ask questions. My questions were answered to my satisfaction. I understand that my participation in this database is voluntary and that I may choose to withdraw at any time. I understand that my decision to participate or withdraw will not affect my future medical treatment. I believe that I have not been unduly influenced by any study team member to participate in the research database. I understand that information regarding my personal health information will be kept confidential, but that absolute confidentiality is not guaranteed. By signing this consent form, I have not waived any of my legal rights. I understand that I will be given a copy of this consent form after signing it.

I freely agree to participate in this research database.

Specifically, I agree to:

Allow my medical chart to be inspected, and to have the information included in the research database. Yes ___ No____ *(initial)*

I agree that my health information collected here may be linked (combined) with other administrative health care information collected by Manitoba Health. Yes ___ No____ *(initial)*

I agree to be contacted about future clinical research studies related to HIV (or related conditions). Yes ___ No____ *(initial)*

By choosing yes, you are only agreeing to review of your medical information to see if you are eligible to participate and to be contacted about participating. For each study you will be given written material including a Consent Form. You may decline if you are not interested.

Participant signature: _____ Date:_____

Participant printed name: _____

If participants cannot read the form themselves, a witness must sign here:

I was present throughout the entire informed consent process with the participant. All questions from the participant were answered and the participant has agreed to take part in the research.

_____ _____

Date Signature of witness

_____

Printed name of witness

If participant does not speak English, an interpreter must sign here:

I was present during the entire consent interview. To the best of my knowledge, I have interpreted the conversation between _____(*the participant*) and _____

(*the interviewer*) accurately.

_____ _____

Date Signature of Interpreter

_____

Printed name of Interpreter

I, the undersigned, have fully explained the relevant details of this research database/registry to the participant named above and or the participant's legally acceptable representative. I believe that the participant or the participant's legally acceptable representative has understood and has knowingly given their consent.

Printed Name: _____ Date:_____

Signature: _____ Role:_____

Table B.2. Informed consent form for participation int he LHIV-Manitoba clinical cohort study, French version.

INFORMATION ET FORMULAIRE DE CONSENTEMENT À L'INTENTION DES PARTICIPANTS À LA RECHERCHE

Titre: Base de données du programme des cliniques de VIH

Vous êtes invité(e) à participer à un projet de base de données de recherche, car vous avez recours au programme des cliniques de VIH du Centre des sciences de la santé ou du Centre de santé communautaire Nine Circles. Dans le cadre des soins de santé que vous recevez, nous conservons un registre de vos visites à la clinique. Nous vous demandons votre consentement afin d'utiliser vos renseignements médicaux pour la recherche et pour l'amélioration de la qualité des soins.

But
Ce projet a pour but de recueillir de l'information sur les personnes touchées par le VIH et les problèmes de santé connexes. Cette information sera conservée dans une base de données. Nous voulons en savoir plus sur vos signes et symptômes liés au VIH, vos antécédents médicaux, l'impact de la maladie, vos autres problèmes de santé et vos traitements. Cette information aidera les chercheurs à en apprendre plus sur le VIH, y compris sur les traitements et les soins.

Nous vous demandons la permission:

De recueillir, conserver et utiliser les renseignements médicaux contenus dans vos dossiers hospitaliers ou cliniques, à des fins de recherche sur le VIH et les problèmes de santé connexes.
D'utiliser vos renseignements médicaux contenus dans les bases de données sur la santé pour effectuer des recherches sur le VIH et les problèmes de santé connexes.
De consulter vos renseignements médicaux provenant des cliniques de VIH afin de déterminer si vous êtes admissible à participer à de futures études de recherche sur le VIH et si vous acceptez que l'on communique avec vous concernant de futures études de recherche sur le VIH.

Marche à suivre
Si vous donnez votre consentement, l'information systématiquement recueillie lorsque vous recevez des soins à la clinique de VIH pourrait servir à la recherche. La participation à cette base de données ne changera en rien le déroulement de vos visites à la clinique. L'information recueillie pour la base de données sera conservée pour toute la durée du programme de lutte contre le VIH. La base de données comprendra les renseignements suivants :

Un chiffre qui remplacera votre nom afin d'assurer la confidentialité de vos renseignements personnels.
De l'information provenant des vos antécédents médicaux et de vos examens physiques.
De l'information concernant les tests et les interventions suivis, comme les analyses sanguines et les radiographies.

Aux fins de la recherche, les renseignements contenus dans cette base de données pourraient être couplés à votre dossier hospitalier ou clinique ou aux renseignements recueillis par Santé Manitoba (données administratives). Ces renseignements peuvent inclure notamment de l'information sur vos hospitalisations, vos consultations médicales et vos ordonnances. Cette information est déjà recueillie dans le cadre de la prestation de services réguliers et ne requiert pas votre consentement. Cependant, votre consentement est nécessaire si des renseignements provenant des bases de données

administratives qui pourraient éventuellement permettre de vous identifier sont utilisés à des fins de recherche.

Le Comité d'éthique de la recherche en santé de l'Université du Manitoba a approuvé cette base de données. Le Comité d'éthique de la recherche en santé de l'Université du Manitoba doit approuver les futures recherches qui feront appel à cette base de données. Les recherches pour lesquelles de l'information provenant des bases de données administratives est utilisée doivent aussi être approuvées par le Comité de la protection des renseignements médicaux de Santé Manitoba.

Personne ne communiquera avec vous ni ne vous avisera en ce qui concerne l'utilisation qui sera faite de vos renseignements. Si vous nous dites que vous êtes intéressé(e) à participer à de futures études de recherche, le personnel de recherche pourrait examiner vos renseignements médicaux pour déterminer si vous répondez aux objectifs des études. Si c'est le cas, on pourrait communiquer avec vous pour vous demander de participer à ces études. Vous pourrez décider alors d'y participer ou non. Vous n'êtes pas obligé(e) de participer à ces études. Vous devrez donner votre consentement pour chaque étude distincte.

Risques et avantages
Il n'y a aucun risque pour la santé lié à la participation à cette base de données de recherche. Il existe toutefois un risque potentiel de perte de confidentialité. Tous les efforts possibles seront faits pour assurer la protection de vos renseignements personnels. Vous ne profiterez peut-être pas directement des études de recherche qui utilisent vos renseignements. Toutefois, ces recherches pourraient permettre de mieux comprendre le VIH et les problèmes de santé connexes et d'améliorer les soins que vous recevrez à l'avenir. Nous espérons que ces recherches seront éventuellement bénéfiques pour les personnes séropositives pour le VIH au Manitoba. Le programme de lutte contre le VIH au Manitoba espère utiliser l'information recueillie dans le cadre de cette étude pour améliorer la prévention du VIH et les soins au Manitoba.

Confidentialité
Tous les renseignements personnels recueillis dans le cadre de cette étude demeureront strictement confidentiels, conformément à la *Loi sur les renseignements médicaux personnels* du Manitoba. Seul le personnel de recherche autorisé aura accès à vos renseignements. Le Comité d'éthique de la recherche en santé de l'Université du Manitoba pourrait examiner des dossiers de la base de données à des fins d'assurance de la qualité.
Votre nom et d'autres renseignements personnels qui pourraient permettre de vous identifier ne seront pas utilisés ni divulgués dans les documents et les présentations concernant le projet de recherche. Les données de recherche seront conservées dans des ordinateurs protégés par mot de passe, dans une zone verrouillée et sécurisée de l'Université du Manitoba. Les documents sur papier seront aussi conservés dans cette zone verrouillée et sécurisée et seuls les chercheurs et leur personnel de recherche y auront accès. Votre nom et les autres renseignements qui pourraient permettre de vous identifier seront retirés des données avant leur analyse. Nous ferons tous les efforts possibles pour assurer la protection de vos renseignements personnels, mais nous ne pouvons pas garantir la confidentialité absolue.

Participation volontaire et retrait de l'étude
Votre décision de participer à la base de données de recherche est volontaire et n'aura aucune incidence sur vos soins médicaux personnels, même si vous refusez de participer à la base de données. Aucune compensation n'est offerte pour la participation. Vous pouvez refuser de participer ou vous retirer de la base de données en tout temps. Si vous choisissez de vous retirer, veuillez communiquer avec le programme de lutte contre le VIH, au 204-xxx-xxxx. Si vous décidez de vous retirer, vos données ne pourront plus être utilisées. Si vous acceptez de participer et que vous changez d'avis par la suite, vos données pourraient déjà avoir été utilisées et analysées.

Questions
Si vous avez des questions concernant la base de données, veuillez communiquer avec le programme de lutte contre le VIH, au 204-xxx-xxxx. Pour les questions concernant vos droits à titre de participant(e) à la recherche, veuillez communiquer avec le bureau du Comité d'éthique de la recherche en santé du Campus Bannatyne de l'Université du Manitoba, au (204) xxx-xxxx.

Déclaration de consentement
J'ai lu et compris le présent formulaire de consentement. En signant le présent formulaire, je donne la permission d'utiliser mes renseignements médicaux personnels à des fins de recherche. J'ai reçu des explications quant à l'utilisation des données recueillies pour cette base de données. J'ai eu amplement de temps et de possibilités pour poser des questions. J'ai reçu des réponses satisfaisantes à mes questions. Je comprends que ma participation à la base de données est volontaire et que je peux choisir de me retirer en tout temps. Je comprends que ma décision de participer ou de me retirer n'aura aucune incidence sur mes futurs traitements médicaux. Je crois ne pas avoir été indûment influencé(e) par l'un ou l'autre des membres de l'équipe de l'étude pour participer à la base de données de recherche. Je comprends que l'information concernant mes renseignements médicaux personnels sera gardée confidentielle, mais que la confidentialité absolue n'est pas garantie. En signant le présent formulaire de consentement, je ne renonce à aucun de mes droits prévus par la loi. Je comprends que je vais recevoir une copie du présent formulaire de consentement après l'avoir signé.

J'accepte de plein gré de participer à cette base de données de recherche. J'accepte expressément ce qui suit :

J'autorise l'examen de mon dossier médical et l'ajout de l'information à la base de données de recherche. Oui ___ Non ____ *(initiales)*

J'accepte que mes renseignements médicaux recueillis ici puissent être couplés (combinés) à d'autres données administratives sur les soins de santé recueillies par Santé Manitoba. Oui ___ Non ____ *(initiales)*

J'accepte que l'on communique avec moi concernant de futures études de recherche clinique liées au VIH (ou les problèmes de santé connexes). Oui ___ Non ____ *(initiales)*

En répondant oui, vous acceptez seulement l'examen de vos renseignements médicaux pour vérifier votre admissibilité à participer et que l'on communique avec vous concernant votre participation. Pour chaque étude, vous recevrez de la documentation écrite, y compris un formulaire de consentement. Vous pourrez alors refuser de participer si vous n'êtes pas intéressé(e).

Signature du participant/de la participante: _____ Date: _____

Nom du participant/de la participante en lettres moulées: _____

Lorsqu'un(e) participant(e) ne peut pas lire le formulaire seul(e), un témoin doit apposer sa signature ci-après:

J'étais présent(e) avec le participant/la participante durant la totalité du processus concernant le consentement éclairé. On a répondu à toutes les questions du participant/de la participante et le participant/la participante a accepté de participer à la recherche.

_____ _____

Date Signature du témoin

_____

Nom du témoin en lettres moulées

Lorsqu'un(e) participant(e) ne parle pas anglais, un interprète doit apposer sa signature ci-après:

J'étais présent(e) durant l'entretien concernant le consentement. À ma connaissance, j'ai interprété fidèlement la conversation entre _____ (*le participant/la participante*) et _____ (*l'intervieweur/intervieweuse*).

_____ _____

Date Signature de l'interprète

_____

Nom de l'interprète en lettres moulées

J'ai, soussigné(e), fourni des explications complètes concernant les détails pertinents de la base de données/du registre de recherche au participant/à la participante susnommé(e) ou à son représentant légal. Je crois que le participant/la participante ou son représentant légal a compris les explications et a donné son consentement éclairé.

Nom en lettres moulées: _____ Date: _____

Signature: _____ Rôle: _____

Appendix C. Supplementary materials for Chapter 3

Table C. 1. Individual-level data collected from the paper and electronic medical records of participants in the LHIV-Manitoba clinical cohort.

VARIABLE	LABEL	CODES	NOTES
SOCIODEMOGRAPHIC CHARACTERISTICS			
Date of birth	DOB	dd-mmm-yy [9999] Unknown	
Date of death	DOD	dd-mmm-yy [7777] Not applicable [9999] Unknown	*If applicable*
Sex	Sex	[1] Male [2] Female [3] Transgender M:F [4] Transgender F:M	
Ethnicity	Eth	[1] Indigenous – Métis [2] Indigenous – Inuit [3] Indigenous – First Nations [4] Indigenous – unspecified [5] white/European [6] Latin American (Hispanic; Mexican; Central American; South American) [7] Sub-Saharan African/Caribbean/Black [9] East/Southeast Asian (Chinese; Korean; Vietnamese; Cambodian; Laotian; Indonesian; Japanese; Filipino) [10] West Asian/North African/Middle Eastern (Afghani; Algerian; Armenian; Azerbaijani; Bahraini; Cypriot; Egyptian; Gaza Strip; Georgian; Iranian; Iraqi; Israeli; Jordanian; Kuwaiti; Lebanese; Libyan; Moroccan; Omani; Palestinian (Gaza Strip and West Bank); Qatari; Saudi; Syrian; Tunisian;	*Self-identified by client*

VARIABLE	LABEL	CODES	NOTES
		Turkish; Emirati; West Bank; Western Saharan; Yemeni) [11] South Asian (Indian; Pakistani; Bangladeshi; Sri Lankan; Nepali; Bhutanese) [9999] Unknown	
Treaty status	Treaty	[0] No [1] Yes [7777] Not applicable [9999] Unknown	
Postal code	Post_Code	X#X#X# [0] No known address [9999] Unknown	*Six digits* *Location of residence at end of 2016*
Regional Health Authority	RHA	[0] No known address [1] Winnipeg Regional Health Authority [2] Brandon [3] Southern Health [4] Prairie Mountain Health [5] Interlake-Eastern Regional Health Authority [6] Northern Health Region [7] Outside of Manitoba [7777] Not applicable [9999] Unknown	*Region of residence at end of 2016.*
OTHER NON-CLINICAL INFORMATION			
Year of immigration to Canada	Immig	yyyy [7777] Not applicable [9999] Unknown	
Has client moved out of province since entering into care with the Manitoba HIV Program	LeftMB	[0] No [1] Yes [9999] Unknown	
Year in which client moved out of province	LeftMB_Date	yyyy [7777] Not applicable [9999] Unknown	

VARIABLE	LABEL	CODES	NOTES
Does client have a primary care provider outside of the Manitoba HIV Program?	GP	[0] No [1] Yes [9999] Unknown	*Primary care provider defined as family physician or nurse practitioner*
NON-HIV CLINICAL INFORMATION			
Active comorbidities			
Type II diabetes	DM	[0] No [1] Yes [6666] Not collected	
Hypertension	HTN	[0] No [1] Yes [6666] Not collected	
Coronary artery disease	CAD	[0] No [1] Yes [6666] Not collected	
Chronic kidney disease	CKD	[0] No [1] Yes [6666] Not collected	
Asthma/COPD	AsthCOPD	[0] No [1] Yes [6666] Not collected	
Congestive heart failure	CHF	[0] No [1] Yes [6666] Not collected	
Co-infections (at or within 6 months of presentation to care, as indicated by date of first CD4 count in Manitoba)			
Cryptococcal meningitis	Crypto	[0] No [1] Yes [6666] Not collected [9999] Unknown	
Date of cryptococcal meningitis diagnosis	Crypto_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	
Oral or esophageal candidiasis (Thrush)	Thrush	[0] No [1] Yes	

VARIABLE	LABEL	CODES	NOTES
		[6666] Not collected [9999] Unknown	
Date of thrush diagnosis	Thrush_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	
Pneumocystis jiroveci pneumonia (PJP)	PJP	[0] No [1] Yes [6666] Not collected [9999] Unknown	
Date of PJP diagnosis	PJP_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	
Mycobacterium Avium-Intracellulare (MAI)	MAI	[0] No [1] Yes [6666] Not collected [9999] Unknown	
Date of MAI diagnosis	MAI_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	
Hepatitis C virus (HCV)	HCV	[0] No [1] Active (Ab+/RNA+) [2] Cleared/treated (Ab+/RNA-) [9999] Unknown	
Date of HCV diagnosis	HCV_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	
Tuberculosis (TB)	TB	[0] No [1] Yes [6666] Not collected [9999] Unknown	
Date of TB diagnosis	TB_Date	dd-mmm-yy	

VARIABLE	LABEL	CODES	NOTES
		[6666] Not collected [7777] Not applicable [9999] Unknown	
Mental health diagnoses			
Schizophrenia	Schiz	[0] No [1] Yes [9999] Unknown	
Date of schizophrenia diagnosis	Schiz_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	
Anxiety	Anx	[0] No [1] Yes [9999] Unknown	
Date of anxiety diagnosis	Anx_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	
Depression	Dep	[0] No [1] Yes [9999] Unknown	
Date of depression diagnosis	Dep_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	
Bipolar disorder	BPD	[0] No [1] Yes [6666] Not collected [7777] Not applicable [9999] Unknown	
Date of bipolar disorder diagnosis	BPD_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	
ADDICTIONS AND SUBSTANCE USE			

VARIABLE	LABEL	CODES	NOTES
Alcohol use			
Alcohol misuse or abuse	EtOH	[0] No [1] Yes [6666] Not collected [7777] Not applicable [9999] Unknown	
Other substance use			
Drug (illicit or prescription) misuse or abuse	Drug	[0] No [1] Yes [6666] Not collected [7777] Not applicable [9999] Unknown	
Type of drugs misused or abused	Drug_Type	[1] Benzodiazepine [2] Alprazolam [3] Clonazepam [4] Diazepam [5] Lorazepam [6] Oxazepam [7] Temazepam [8] Tylenol 3 [9] Cocaine [10] Solvents [11] Percocet [12] Heroin [13] Methadone [14] Crystal methamphetamine [15] Morphine [16] Oxycontin/Oxyneo [17] Talwin & Ritalin [18] Hydromorphone (Dilaudid) [19] Ecstasy [20] Tramadol [21] Buprenorphine [22] Unspecified opioids [23] Unspecified hallucinogens	*Select all that apply*

VARIABLE	LABEL	CODES	NOTES
		[24] Fentanyl [25] Codeine Contin [26] MDMA [27] Morphine (MS Contin) [28] Lysergic acid diethylamide (LSD) [29] Gamma-hydroxybutyrate (GHB) [30] Ketamine [31] Crack cocaine [32] Poppers (alkyl nitrates) [6666] Not collected [7777] Not applicable [9999] Unknown	
Injection drug use	IDU	[0] No [1] Yes [6666] Not collected [7777] Not applicable [9999] Unknown	
HIV-SPECIFIC CLINICAL INDICATORS			
HIV diagnosis and exposure categories			
Date of HIV diagnosis	HIVDiag_Date	dd-mmm-yy [9999] Unknown	*If day not known, estimate midpoint of month. If month and day unknown estimate 30 June.*
Was first positive HIV test performed in Manitoba?	HIVDiag_MB	[0] No [1] Yes [9999] Unknown	
Place of first HIV+ test if outside of Manitoba	HIVDiag_Place	[1] Québec [2] Ontario [3] Kenya [4] Saskatchewan [5] British Columbia [6] Alberta [7] Taiwan [8] South Korea [9] Ghana	*Within Canada, report province. Outside of Canada, report country.*

VARIABLE	LABEL	CODES	NOTES
		[10] Australia [11] Haiti [12] New Brunswick [13] Philippines [14] Rwanda [15] Malaysia [16] Bahamas [17] Uganda [18] Nigeria [19] Congo [20] Nova Scotia [21] United States of America [22] South Africa [23] Belgium [24] United Kingdom [25] India [26] Vietnam [27] Jamaica [28] Egypt [29] Ethiopia [30] Somalia [31] Eritrea [32] Zambia [33] Cameroon [34] Burundi [7777] Not applicable [9999] Unknown	
Self-identified HIV exposure category	HIVExp	[1] Unprotected heterosexual contact [2] Unprotected sex between men (MSM) [3] Injection drug use [4] Originally from an HIV endemic country [5] Occupational exposure [6] Recipient of blood/blood products [7] Other [8] Perinatal acquisition	*Select all that apply. [4] should not be selected alone.*

VARIABLE	LABEL	CODES	NOTES
		[9999] Unknown	
CD4 counts			
First CD4 count in Manitoba	InitCD4	Numeric value [6666] Not collected [7777] Not applicable [9999] Unknown	*Recorded as whole number.* *If CD4 [<35] in EMR, entered as [0] in database.*
First CD4% in Manitoba	InitCD4p	Numeric value [6666] Not collected [7777] Not applicable [9999] Unknown	*Recorded as whole number*
Date of first CD4/CD4% in Manitoba	InitCD4_Date	dd-mmm-yy [[6666] Not collected [7777] Not applicable [9999] Unknown	
Ever on antiretroviral therapy (ART)	ART	[0] No [1] Yes [9999] Unknown	
First recorded date of ART start	ART_Date	dd-mmm-yy [7777] Not applicable [9999] Unknown	
Last CD4 count before first recorded ART start	ARTCD4	Numeric value [7777] Not applicable [9999] Unknown	
Last CD4% before first recorded ART start	ARTCD4p	Numeric value [7777] Not applicable [9999] Unknown	
Date of last CD4/CD4% test before first recorded ART start	ARTCD4_Date	dd-mmm-yy [7777] Not applicable [9999] Unknown	
Most recent CD4 count	16CD4	Numeric value [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of 2016.*
Most recent CD4%	16CD4p	Numeric value [6666] Not collected	*Up to end of 2016.*

VARIABLE	LABEL	CODES	NOTES
		[7777] Not applicable [9999] Unknown	
Date of most recent CD4/CD4%	16CD4_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of 2016.*
Most recent CD4 count	17CD4	Numeric value [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of 2017.*
Most recent CD4%	17CD4p	Numeric value [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of 2017.*
Date of most recent CD4/CD4%	17CD4_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of 2017.*
Most recent CD4 count	Q218CD4	Numeric value [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of June 2018 (Q2).*
Most recent CD4%	Q218CD4p	Numeric value [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of June 2018 (Q2).*
Date of most recent CD4/CD4%	Q218CD4_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of June 2018 (Q2).*
Most recent CD4 count	Q418CD4	Numeric value [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of December 2018 (Q4).*

VARIABLE	LABEL	CODES	NOTES
Most recent CD4%	Q418CD4p	Numeric value [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of December 2018 (Q4).*
Date of most recent CD4/CD4%	Q418CD4_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	*Up to end of December 2018 (Q4).*
Viral loads			
Viral load test result	InitVL	Numeric value. [0] Undetectable VL (TND; Target not detected; No HIV-1 RNA detected;<20 cp;<2.00E+1;<40; <50; etc.) [6666] Not collected [7777] Not applicable [9999] Unknown (Not done; Too long; Too long in trans; TLIT; Cancelled; Error; Deleted; Redraw; Recollect; Repeat; Sample too old; Resubmit sample <24h old; Insufficient sample; etc.)	*First viral load test result entered into Accuro at Health Sciences Centre OR first test result in 2016 at Nine Circles.*
Date of viral load test	InitVL_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	*Specimen collection date associated with initial viral load test.*
Viral load test result	Q416VL	Numeric value. [0] Undetectable VL (TND; Target not detected; No HIV-1 RNA detected;<20 cp;<2.00E+1;<40; <50; etc.) [6666] Not collected [7777] Not applicable [9999] Unknown (Not done; Too long; Too long in trans; TLIT; Cancelled; Error; Deleted; Redraw; Recollect; Repeat; Sample too old; Resubmit sample <24h old; Insufficient sample; etc.)	*Last viral load test result, up to the end of December 2016 (Q4).*

VARIABLE	LABEL	CODES	NOTES
Date of viral load test	Q416VL_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	*Specimen collection date associated with last viral load test.* *Up to the end of December 2016 (Q4).*
Viral load test result	Q217VL	Numeric value. [0] Undetectable VL (TND; Target not detected; No HIV-1 RNA detected;<20 cp;<2.00E+1;<40; <50; etc.) [6666] Not collected [7777] Not applicable [9999] Unknown (Not done; Too long; Too long in trans; TLIT; Cancelled; Error; Deleted; Redraw; Recollect; Repeat; Sample too old; Resubmit sample <24h old; Insufficient sample; etc.)	*Last viral load test result, up to the end of June 2017 (Q2).*
Date of viral load test	Q217VL_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	*Specimen collection date associated with last viral load test.* *Up to the end of June 2017 (Q2).*
Viral load test result	Q417VL	Numeric value. [0] Undetectable VL (TND; Target not detected; No HIV-1 RNA detected;<20 cp;<2.00E+1;<40; <50; etc.) [6666] Not collected [7777] Not applicable [9999] Unknown (Not done; Too long; Too long in trans; TLIT; Cancelled; Error; Deleted; Redraw; Recollect; Repeat; Sample too old; Resubmit sample <24h old; Insufficient sample; etc.)	*Last viral load test result, up to the end of December 2017 (Q4).*
Date of viral load test	Q417VL_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	*Specimen collection date associated with last viral load test.* *Up to the end of December 2017 (Q4).*

VARIABLE	LABEL	CODES	NOTES
Viral load test result	Q218VL	Numeric value. [0] Undetectable VL (TND; Target not detected; No HIV-1 RNA detected;<20 cp;<2.00E+1;<40; <50; etc.) [6666] Not collected [7777] Not applicable [9999] Unknown (Not done; Too long; Too long in trans; TLIT; Cancelled; Error; Deleted; Redraw; Recollect; Repeat; Sample too old; Resubmit sample <24h old; Insufficient sample; etc.)	*Last viral load test result, up to the end of June 2018 (Q2).*
Date of viral load test	Q218VL_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	*Specimen collection date associated with last viral load test.* *Up to the end of June 2018 (Q2).*
Viral load test result	Q418VL	Numeric value. [0] Undetectable VL (TND; Target not detected; No HIV-1 RNA detected;<20 cp;<2.00E+1;<40; <50; etc.) [6666] Not collected [7777] Not applicable [9999] Unknown (Not done; Too long; Too long in trans; TLIT; Cancelled; Error; Deleted; Redraw; Recollect; Repeat; Sample too old; Resubmit sample <24h old; Insufficient sample; etc.)	*Last viral load test result, up to the end of December 2018 (Q4).*
Date of viral load test	Q418VL_Date	dd-mmm-yy [6666] Not collected [7777] Not applicable [9999] Unknown	*Specimen collection date associated with last viral load test.* *Up to the end of December 2018 (Q4).*
HIV MEDICATION INFORMATION			
Antiretroviral therapy regimen			
	Q217ART_Name	[1] Abacavir [2] Triumeq	*Select all that apply.* *Up to end of June 2017 (Q2).*

VARIABLE	LABEL	CODES	NOTES
Name(s) of antiretroviral drugs (ARVs) included in active prescription.		[3] Kivexa [4] Reyataz	*Most common trade names listed for each medication.*
	Q417ART_Name	[5] Prezista [6] Prezcobix [7] Tivicay [8] Sustiva [9] Atripla	*Select all that apply.* *Up to end of December 2017 (Q4).* *Most common trade names listed for each medication.*
	Q218ART_Name	[10] Genvoya [11] Stribild [12] Complera [13] Descovy	*Select all that apply.* *Up to end of June 2018 (Q2).* *Most common trade names listed for each medication.*
	Q418ART_Name	[14] Truvada [15] Intelence [16] Telzir [17] 3TC [18] Combivir [19] Kaletra [20] Viracept [21] Isentress [22] Edurant [23] Norvir [24] Viread [25] Viramune [26] Study medication [27] Odefsey [28] Celsentri [29] Biktarvy [30] Juluca [6666] Not collected [7777] Not applicable/Not on treatment [9999] Unknown	*Select all that apply.* *Up to end of December 2018 (Q4).* *Most common trade names listed for each medication.*
Class(es) of ARVs included in active prescription.	Q217ART_Class	[1] Entry inhibitor [2] Integrase inhibitor (INI) [3] Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI)	*Select all that apply.* *Up to end of June 2017 (Q2).* *Note: Combination HIV Medicines/Single Tablet*

VARIABLE	LABEL	CODES	NOTES
		[4] Nucleos(t)ide Reverse Transcriptase Inhibitor (NRTI) [5] NRTI: Combination products [6] Protease inhibitor (PI)	*Regimen (STR) products contain at least two different classes of antiretroviral medication in one pill.*
	Q417ART_Class	[7] Combination HIV Medicines/Single Tablet Regimen (STR) products [8] Pharmacokinetic enhancers [6666] Not collected [7777] Not applicable/Not on treatment [9999] Unknown	*Select all that apply.* *Up to end of December 2017 (Q4).* *Note: Combination HIV Medicines/Single Tablet Regimen (STR) products contain at least two different classes of antiretroviral medication in one pill.*
	Q218ART_Class		*Select all that apply.* *Up to end of June 2018 (Q2).* *Note: Combination HIV Medicines/Single Tablet Regimen (STR) products contain at least two different classes of antiretroviral medication in one pill.*
	Q418ART_Class		*Select all that apply.* *Up to end of December 2018 (Q4).* *Note: Combination HIV Medicines/Single Tablet Regimen (STR) products contain at least two different classes of antiretroviral medication in one pill.*
Pharmaceutical insurance coverage			
Pharmaceutical coverage	Coverage16	[0] None [1] Canadian Forces Health Services (CFHS) [2] Clinical trial [3] Compassionate coverage	

VARIABLE	LABEL	CODES	NOTES
		[4] Employment and Income Assistance (EIA) [5] Interim Federal Health (IFH) [6] Non-Insured Health Benefits (NIHB; Treaty) [7] Pharmacare-Manitoba [8] Private insurance [9] Corrections [10] Out of province insurance [6666] Not collected [7777] Not applicable [9999] Unknown	
	Coverage17	[0] None [1] Canadian Forces Health Services (CFHS) [2] Clinical trial [3] Compassionate coverage [4] Employment and Income Assistance (EIA) [5] Interim Federal Health Program (IFHP) [6] Non-Insured Health Benefits (NIHB; Treaty) [7] Pharmacare-Manitoba [8] Private insurance [9] Corrections [10] Out of province insurance [6666] Not collected [7777] Not applicable [9999] Unknown	
	CoverageQ218	[0] None [1] Canadian Forces Health Services (CFHS) [2] Clinical trial [3] Compassionate coverage [4] Employment and Income Assistance (EIA) [5] Interim Federal Health (IFH) [6] Non-Insured Health Benefits (NIHB; Treaty) [7] Pharmacare-Manitoba [8] Employer drug plan (Patient) [9] Employer drug plan (Spouse/Partner) [10] Employer drug plan (Patient & Spouse/Partner)	*As of 26 July 2018*

VARIABLE	LABEL	CODES	NOTES
		[11] Corrections [12] Out of province insurance [13] Other [6666] Not collected [7777] Not applicable [9999] Unknown	
	CoverageQ418	[0] None [1] Canadian Forces Health Services (CFHS) [2] Clinical trial [3] Compassionate coverage [4] Employment and Income Assistance (EIA) [5] Interim Federal Health (IFH) [6] Non-Insured Health Benefits (NIHB; Treaty) [7] Pharmacare-Manitoba [8] Employer drug plan (Patient) [9] Employer drug plan (Spouse/Partner) [10] Employer drug plan (Patient & Spouse/Partner) [11] Corrections [12] Out of province insurance [13] Other [6666] Not collected [7777] Not applicable [9999] Unknown	*As of 10 January 2019*

Table C. 2. Provincial administrative health databases used in Manitoba's LHIV clinical cohort.

DATABASE NAME	DESCRIPTION*	VARIABLES EXTRACTED
Manitoba Health Insurance Registry	Population-based registry of all individuals registered (health insurance) with Manitoba Health, Seniors and Active Living at some point since 1970. Data updated annually.	PHIN (scrambled); Sex; Date of birth; Death; Status (alive or migrated); Location of residence (FSA); RHA, Community, Neighbourhood clusters, rural district, muncd, Province, Record year; Coverage date; Cancellation date; Year of record; Date of death/migration
Medical Claims (Physician Billings)	Contains information (diagnoses, visit date, physician code, billing codes, etc.) from all ambulatory visits (in offices, hospitals, and outpatient departments) to physicians; fee-for-service components for tests (labs, x-ray) performed in offices and hospitals; shadow billing records, etc.	PHIN (scrambled); Date of birth; Sex; Geographic region of residence; Date of services (SAS); Physician characteristics (MD and clinic); Diagnosis codes; Tariff codes; MD_Bloc; MD_Sub_Bloc
Hospital Separation abstracts	Contains demographic and clinical information from in-patient stays in hospitals in Manitoba, as completed at time of discharge.	PHIN (scrambled); Date of birth; Sex; Geographic region of residence; Date of admission; Date of discharge; Length of stay; Hospital number; diagnosis codes; Procedure codes; Procedure date; Disposal (e.g., discharge status, etc.)
Drug Program Information Network (DPIN)	Contains information from all pharmaceutical dispensations in Manitoba, regardless of insurance coverage or final payer.	PHIN (scrambled); Date service provided (claimdtnm); Current prescription number for claim (currxno); Original prescription number for claim (orgxno); Date claim was processed (procyymm); Adjudication (adjud); Number of refills remaining on prescription (refilled); Therapeutic class of DIN (thclass); Days supply on prescription (supply); DIN

DATABASE NAME	DESCRIPTION*	VARIABLES EXTRACTED
Manitoba Health Sexually Transmitted and Blood-Borne Infection (STBBI) Database	Contains information on all positive cases of chlamydia, gonorrhoea, and syphilis, as reported to Manitoba Health, Seniors and Active Living, including cases not tested through Cadham Provincial Laboratory. Also includes positive HIV tests.	PHIN (scrambled); Date of birth; Gender; ICD91; ICD92; Specimen date; Result1; Result2; Result3; Symptom1; Symptom2; Syphilis; Site1; Site2; Site3; Spec1dt; Spec2dt; Spec3dt; Gonorrhea notification; Reqnum1; Reqnum2; Reqnum3; Test1; Test2; Test3; treated1; treated2; TB diagnosis date; TB diagnosis site; Country of origin; Treatment outcomes
Cadham Provincial Laboratory	Includes almost all diagnostic tests and screens (positive and negative) in Manitoba related to microbiology, serology, parasitology, and virology (including STBBIs).	For chlamydial/gonorrheal specimens, hepatitis C, syphilis, herpes simplex virus, HIV antibody, and HIV viral load: PHIN (scrambled); Date of birth; Sex; Lab request number (reqnum); Referral facility (refer_facil); Received date (recd_dt); Specimen date (spec_dt); Login date; Test type; Result; Year of birth month of birth

*All information retrieved from the Manitoba Centre for Health Policy website [213].

Table C. 3. Patterns of missing values among key clinical outcome variables within the LHIV-Manitoba clinical cohort dataset.

Initial CD4 count in Manitoba	Last CD4 count, up to end of 2018	Initial viral load	Last viral load, up to end of 2018	Frequency
Complete	Complete	Complete	Complete	809
Complete	Complete	Missing	Missing	35
Complete	Complete	Complete	Missing	29
Missing	Complete	Complete	Complete	8
Missing	Complete	Missing	Missing	3
Missing	Missing	Missing	Missing	3
Complete	Missing	Complete	Complete	1
Complete	Missing	Complete	Missing	1
Missing	Missing	Complete	Complete	1

Table C. 4. Proportion of missing values among key clinical outcome variables within the LHIV-Manitoba clinical cohort dataset, by age group.

	Age range (years) on March 31, 2019 or at time of death										
	18-24 (*N* = 10)		**25-39 (*N* = 178)**		**40-64 (*N* = 621)**		**≥65 (*N* = 81)**		**Total (*N* = 890)**		***p*-value**
Missing value	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	
Initial CD4 count in Manitoba	0	0	3	1.7	10	1.6	2	2.5	15	1.7	0.920
Last CD4 count, up to end of 2018	0	0	2	1.1	4	0.6	0	0	6	0.7	0.762
Initial viral load	1	10.0	10	5.6	27	4.4	3	3.7	41	4.6	0.724
Last viral load, up to end of 2018	1	10.0	17	9.6	44	7.1	9	11.1	71	8.0	0.491

Table C. 5. Proportion of missing values among key clinical outcome variables within the LHIV-Manitoba clinical cohort dataset, by sex.

	Sex						
	Male (*N* = 634)		Female (*N* = 245)		Total (*N* = 890)		p-value
Missing value	*n*	%	*n*	%	*n*	%	
Initial CD4 count in Manitoba	10	1.6	5	2.0	15	1.7	0.693
Last CD4 count, up to end of 2018	3	0.5	3	1.2	6	0.7	0.249
Initial viral load	33	5.2	8	3.1	41	4.6	0.180
Last viral load, up to end of 2018	52	8.2	19	7.4	71	8.0	0.697

Table C. 6. Proportion of missing values among key clinical outcome variables within the LHIV-Manitoba clinical cohort dataset, by ethnicity.

	Self-identified ethnicity										
	Indigenous (*N* = 369)		**White (*N* = 376)**		**Sub-Saharan African/ Caribbean/ Black (*N* = 97)**		**Other (*N* = 44)**		**Total (*N* = 890)**		***p*-value**
Missing value	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	
Initial CD4 count in Manitoba	4	1.1	8	2.1	0	0	0	0	12	1.4	0.282
Last CD4 count, up to end of 2018	2	0.5	1	0.3	0	0	0	0	3	0.3	0.840
Initial viral load	18	4.9	15	4.0	0	0	5	11.4	38	4.3	0.018
Last viral load, up to end of 2018	28	7.6	26	6.9	7	7.2	7	15.9	68	7.7	0.208

Table C. 7. Proportion of missing values among key clinical outcome variables within the LHIV-Manitoba clinical cohort dataset, by geography.

	Region of residence (by health region)																
	Winnipeg (*N* = 719)		**Eastern (*N* = 48)**		**Southern (*N* = 37)**		**Western (*N* = 35)**		**Northern (*N* = 30)**		**Out of province (*N* = 12)**		**Unknown/ No known address (*N* = 9)**		**Total (*N* = 890)**		***p*-value**
Missing value	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*N*	%	
Initial CD4 count in Manitoba	11	1.5	0	0	0	0	1	2.9	0	0	0	0	3	33.3	15	1.7	0.000
Last CD4 count, up to end of 2018	2	0.3	0	0	0	0	1	2.9	0	0	0	0	3	33.3	6	0.7	0.000
Initial viral load	27	3.8	0	0	0	0	5	14.3	2	6.7	3	25.0	4	44.4	41	4.6	0.000
Last viral load, up to end of 2018	54	7.5	1	2.1	1	2.7	5	14.3	3	10.0	3	25.0	4	44.4	71	8.0	0.000

Table C. 8. Proportion of participants enrolled in prescription drug plans with and without associated out-of-pocket expenses.

	Out-of-pocket expenses associated with drug plan?		*n*	%
	No	**Yes**		
Federally funded insurance schemes				
Canadian Forces Health Services	✓		2	0.3
Non-Insured Health Benefits	✓		206	30.4
Provincially funded insurance schemes				
Employment and Income Assistance	✓		140	20.7
Manitoba Pharmacare		✓	170	25.1
Other insurance schemes				
Private (third-party) insurance		✓	127	18.8
Corrections	✓		8	1.2
Out of province drug plan		✓	2	0.3
No insurance		✓	3	0.4
Clinical trial	✓		9	1.3
Industry-funded “compassionate access” program	✓		10	1.5
TOTAL	**375 (55.4)**	**302 (44.6)**	**677**	**100**

Appendix D. Supplementary materials for Chapter 4

Table D.1. Raw data corresponding to Figure 4.2: Number of cohort participants in each HIV care cascade step when different indicator definitions with varying stringencies are used.

	HIV CARE CASCADE STEP				
Definition stringency	***Alive and diagnosed***	***In care***	***Retained in care***	***On treatment***	***Virologically suppressed***
Lenient definition		659	563	630	574
Lenient definition + physician visit data		663	631		
Moderate definition	703	602	548	618	499
Moderate definition + physician visit data	-	638	612	-	-
Conservative definition	-	386	-	584	487
Conservative definition + physician visit data	-	518	-	-	-

Table D.2. Raw data corresponding to Figure 4.3: Number and proportion of cohort participants in each HIV care cascade step, and proportion of participants lost from the previous cascade step.

HIV care cascade step	***n***	**Proportion (%) of *Alive and diagnosed***	**Proportion (%) lost from previous step**
Alive and diagnosed	703	100	-
In care	638	90.8	9.2
Retained in care	606	86.2	4.6
On treatment	573	81.5	4.7
Virologically suppressed, among on treatment	523	74.4	7.1
Virologically suppressed, among retained in care	536	76.2	10.0