

HERPES AND HIV CO-INFECTION AND  
QUALITY OF LIFE IN WOMEN



EXPLORING THE RELATIONSHIP BETWEEN HSV-2/HIV CO-INFECTION  
AND  
HEALTH-RELATED QUALITY OF LIFE  
OF ADULT HIV-POSITIVE WOMEN:  
A MIXED METHODS STUDY

By

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### **Abstract**

**Background:** The life-time prevalence of HSV-2 is higher in people infected with HIV/AIDS compared to the general population. Little is known about the experiences of women living with these two chronic sexually transmitted viral infections (STVIs), for example, whether HSV-2/ HIV co-infection complicates women's experiences and influences their perceived health-related quality of life (HRQoL). The degree to which HSV-2/HIV co-infection changes perceived physical and mental HRQoL of HIV-positive women when taking into account other factors related to HRQoL including the degree of immunosuppression, demographic characteristics, and co-existent psychological issues is not known. It has not been investigated whether these two chronic STVIs create additional challenges in social and sexual relationships for women. It is also not understood if body image or self-esteem are complicated by HSV-2/HIV co-infection, as well as how women perceive and experience disclosure in relationships and stigma. No quantitative or qualitative studies have explored these phenomena in a Canadian HIV-positive female population.

**Methods:** This mixed methods study explored the association between HIV/ HSV-2 co-infection and physical and mental HRQoL of adult HIV-positive women. A sequential exploratory model was utilized, which involved collecting qualitative data after a quantitative phase. In the first quantitative phase, a cross-sectional questionnaire was administered, HSV-2 sero-status was determined and clinical correlates and HRQoL scores were analyzed using multivariable methods. The second qualitative phase was conducted to further explain the quantitative findings; participants' views of the relationship between symptomatic HSV-2 and HIV co-infection and HRQoL were

explored. The qualitative phase employed an interpretive phenomenological philosophy and methodology.

**Quantitative Findings:** Although women's HRQoL scores on general and HIV-specific measures differed depending on their HSV-2 sero-status, place of origin, receipt of antiretroviral therapy, etc., HSV-2/HIV co-infected women did not have significantly different HRQoL scores compared to women infected with HIV alone. This conclusion was drawn on the basis of only fair goodness-of-fit of the linear regression models.

HSV-2 sero-positivity predicting a better perceived physical and mental HRQoL was also considered biologically implausible and divergent with the literature.

**Qualitative Findings:** The participant narratives highlighted the meaning that women ascribe to living with HIV and HSV-2 in relationship to their perceived HRQoL. HIV was something that affected their global physical and mental HRQoL; it was associated with a social and historical context and was mapped onto their life trajectories. HSV-2, on the other hand, was an immediate concern experienced on an episodic basis, and was more relevant to dimensions of HRQoL such as day-to-day physical and social functioning, as well as intimacy and relationships with partners. HSV-2 infection was a separate, dominant and gendered medical condition that compounded and complicated women's experiences with HIV.

**Main implication:** HRQoL assessments from the perspective of patients will become increasingly important as life-prolonging antiretroviral treatments are refined and clinicians and HIV-positive individuals look to maximize quality of life and well-being. As people living with HIV/AIDS continue to face complex health-related challenges, it is essential to incorporate HRQoL into treatment and care planning. It is important for

service providers to account for HSV-2 as an important medical and psychosocial issue and to discuss with their clients how HSV-2 may affect perceived HRQoL. This study adds to the body of knowledge regarding women's experiences living with HIV, but adds an important layer regarding co-infections and co-morbidities, which are relevant to developing an understanding of women's sexual health.

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### List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
CMV	Cytomegalovirus
HAART	Highly active antiretroviral therapy
HADS	Hospital Anxiety and Depression Scale
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HRQoL	Health-related quality of life
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simplex virus type 2
ICC	Intraclass correlation coefficient
MHS	Mental health summary score
MOS-HIV	Medical Outcomes Study HIV Health Survey
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OR	Odds ratio
PHS	Physical health summary score
PI	Protease inhibitor
R <sup>2</sup>	Coefficient of determination
SF-12v2	Short Form 12 version 2
SF-36	Short Form 36
SIS	Special Immunology Services
STVIs	Sexually transmitted viral infections

## **Chapter 1**

### **Background and rationale for exploring HSV-2/HIV co-infection and health-related quality of life and employing mixed methods**

HIV/AIDS has evolved since the 1980s; the infection is now considered a chronic illness that can be effectively managed with highly active anti-retroviral therapy (HAART). This paradigm shift has resulted from a significant decline in HIV-related morbidity and mortality across the globe. It is recognized however that people living with HIV/AIDS continue to face complex medical demands and social challenges as they age with the disease. It is believed that these health-related challenges, which include co-morbid health conditions such as cancer, cardiovascular disease, psychological complications or mental illness and co-infections, may affect perceived quality of life and overall well-being. In light of this, provincial and national HIV funding bodies, for example the Canadian Institutes of Health Research, have identified co-infections and co-morbidities as priorities for study<sup>1</sup> and these issues are increasingly being showcased and debated at provincial and national HIV research conferences including those hosted by the Ontario HIV Treatment Network and the Canadian Association for HIV Research. In the following chapter, I will discuss health-related quality of life as a construct and how it relates to infection with HIV. I will then discuss co-infection with HIV and herpes simplex virus type 2 and how this may relate to health-related quality of life in women, along with the relevant research topics that this thesis explores.

## **1.0 Background and rationale**

### ***1.1 Health-related quality of life as a construct***

Health-related quality of life (HRQoL) is a patient-reported outcome that measures an aspect of a person's health status incorporating a multitude of dimensions including physical function and symptoms, performance of social roles and social well-being, psychological or emotional status, cognitive functioning, and how the patient feels about their health.<sup>2-4</sup> Patrick and Erickson broadly define HRQoL as the “value assigned to the duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy.”<sup>5</sup> Shumaker provides another perspective stating that HRQoL is often defined as the subjective experiences of individuals participating in research studies, and is not necessarily an observable entity.<sup>6</sup>

Some HRQoL questionnaires have employed a model of needs fulfillment in order to numerically capture health status. For example, the Recurrent Genital Herpes Quality of Life questionnaire postulates that “life gains its quality from the ability and capacity of the individual to satisfy his or her needs.”<sup>7</sup> In interpreting HRQoL scores, this can be understood that when a HRQoL score is high, the needs are fulfilled, whereas when a HRQoL score is low, few needs have been satisfied. The needs-based model is well-established and has been applied successfully in the development of other disease-specific quality of life measures.<sup>8-10</sup>

## ***1.2 Measuring HRQoL***

HRQoL is important for measuring the impact of chronic disease.<sup>5,11</sup> Each HRQoL questionnaire is comprised of items or questions that are added up in a number of domains or dimensions related to behaviour or experience of interest.<sup>11</sup> HRQoL instruments are typically used to: (1) differentiate between people who have a better HRQoL compared to those with a worse HRQoL, that is, a discriminative measure; and (2) understand how HRQoL has changed over time, that is, an evaluative measure.<sup>11</sup> Generic instruments exist that can be applied to a variety of populations enabling broad comparisons of the relative impact of different health-related interventions. Generic instruments may measure health profiles or utility, for example, the net impact on quantity and quality of life or cost-utility analysis. These generic instruments, however, may be unresponsive to changes in specific conditions or populations. Specific HRQoL instruments exist, which focus on particular aspects of health status in a disease, population, function or problem of interest. These specific instruments increase the likelihood of improved responsiveness and understanding of differences in HRQoL between groups (i.e. discriminative measure) or changes over time (i.e. evaluative measure) in a particular context.<sup>11</sup>

## ***1.3 Measuring HRQoL in HIV infection***

### ***1.3.1 Medical Outcomes Study – HIV Health Survey (MOS-HIV)***

The MOS-HIV is a 35-item HIV-specific questionnaire that includes ten dimensions of HRQoL including general health perceptions, bodily pain, physical functioning, role functioning, social functioning, cognitive functioning, mental health,

energy/vitality, health distress and health transition allowing for the generation of physical (PHS) and mental (MHS) health summary scores.<sup>12-16</sup> Development of the MOS-HIV began in 1987 and items selected from the SF-20, another quality of life measure, were the foundation for its construction.<sup>12-14</sup> The MOS-HIV was developed to provide a brief, comprehensive measure of functional status and well-being of people living with HIV/AIDS enrolled in large-scale clinical trials and has been shown to be internally consistent and responsive to a number of outcomes including infections, adverse events, increased symptoms and AIDS-related events.<sup>13-15</sup> The MOS-HIV has also been used in studies with a variety of patient groups ranging from treatment-naïve and asymptomatic people living with HIV/AIDS to those with more advanced HIV and opportunistic infections. Data from numerous studies support the internal consistency of the multi-item scales in the MOS-HIV.<sup>14</sup> Revicki et al. (1998) demonstrated the internal consistency of the PHS ranging from 0.90 to 0.92 and the MHS ranging from 0.91 to 0.94 in observational cohort studies and clinical trials, respectively, as measured by Cronbach's alpha correlation coefficient.<sup>16</sup> Studies exploring the test-retest reliability of the MOS-HIV have not been as favourable as those demonstrating high internal consistency. In an observational cohort study by Revicki et al, which sought to examine changes in health status and clinical condition over time and the measurement characteristics of health status and health utility measures in HIV disease populations, a test-retest reliability, as measured by intraclass correlation coefficients (ICC), of 0.72 was observed for the PHS and 0.60 was observed for the MHS.<sup>16</sup> In this observational cohort study, test-retest reliability was measured after a 4-month follow-up; 44% of participants had AIDS, 31% had symptomatic HIV, and 25% had asymptomatic HIV infection.<sup>17</sup> A



moderate test-retest reliability may have been observed in this cohort study because of the 4-month interval between measures. Since the MOS-HIV asks individuals to describe their HRQoL in the past 4 weeks, it would have been more favourable to conduct the follow-up visit about 2 to 4 weeks after the baseline visit. This timeframe between study visits would have ensured that participants were not asked to consider nearly the same 4-week period on both occasions and not too much time would have lapsed in which HRQoL scores may have drastically changed.<sup>18</sup> Revicki et al. observed changes in different dimensions of health status depending on the stage of HIV-disease over the 4-month follow-up period. For example, the non-AIDS groups tended to have larger changes in psychological functioning and role function compared to the group living with AIDS. Revicki et al. proposed that a 4-month follow-up would be useful to assess changes in health status or clinical conditions in those living with AIDS, but that a 6 to 12-month interval would be more appropriate to observe changes in asymptomatic or symptomatic HIV-infected people.<sup>17</sup> Badia and colleagues also assessed the test-retest reliability of the MOS-HIV in a sample of 98 HIV-positive men and women who were clinically stable on antiretroviral treatment and who had completed the MOS-HIV on two occasions, two weeks apart.<sup>19</sup> Although the interval for administering the HRQoL measure was appropriate, the MOS-HIV had poor to moderate test-retest reliability with ICCs ranging from 0.24 to 0.85. The ICC was 0.58 for the PHS and 0.85 for the MHS; ICCs were satisfactory, i.e. greater than 0.7, for all MOS-HIV sub-scales except for the pain, physical functioning, role function, social functioning, quality of life and health transition sub-scales. The authors cited uncertainty about the course of HIV infection and

compliance with antiretroviral therapy as factors that may have contributed to the poor test-retest reliability, even in a cohort of relatively stable patients.<sup>19</sup>

### 1.3.2. SF-12v2

The SF-12v2 is a generic measure of HRQoL which was derived from and reflects the same 8 sub-domains as the SF-36 including physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. These domains or dimensions are combined to generate two similar HRQoL summary scores, the PHS and MHS.<sup>20</sup> Construction of the SF-12 arose from two data sources including the National Survey of Functional Health Status, a cross-sectional survey used to gather norms for the SF-36 Health Survey, and the Medical Outcomes Study, an observational study of adults with chronic medical conditions, including HIV/AIDS. The 12 items chosen for the SF-12 achieved a multiple  $R^2$  value of 0.911 and 0.918 in predicting the PHS and MHS of the SF-36, respectively.<sup>20</sup> Test-retest reliability of the SF-12 PHS ranged from 0.86 to 0.89 in the data sources whereas the SF-12 MHS ranged from 0.76 to 0.77, which compared favourably with the eight common items in the SF-36. Although the SF-12v2 has never been truly validated in an HIV population, the SF-36 that it was derived from has been shown to have excellent psychometric properties in many disease areas including HIV/AIDS.<sup>15</sup> In HIV research studies, the SF-36 demonstrates good internal consistency, reliability, construct validity and responsiveness to initiation of HIV treatment, change in CD4 cell count, viral load and other symptoms.<sup>15</sup>

Ion et al. demonstrated the MOS-HIV and SF-12v2 to be positively correlated with regard to both the PHS and MHS respectively ( $r=0.84$ ,  $p<0.001$  and  $r=0.76$ ,  $p<0.001$ ).<sup>21</sup> A comparison of the MOS-HIV and SF-12v2 common domains including physical functioning (PF), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF) and mental health (MH) yielded positive correlations for all categories (PF:  $r=0.90$ ; BP:  $r=0.82$ ; GH:  $r=0.80$ ; VT:  $r=0.72$ ; SF:  $r=0.68$ ; MH:  $r=0.58$ ; all significant at  $p<0.001$ ). The domains role physical (RP) and role emotional (RE) of the SF-12v2 were compared separately to the domain role functioning of the MOS-HIV yielding slightly lower, yet positive correlations (RP:  $r=0.69$ ; RE:  $r=0.49$ ;  $p<0.001$ ). The MOS-HIV and SF-12v2 also demonstrated substantial agreement for assigning individuals to specific states of HRQoL based on their MOS-HIV PHS and MHS with weighted  $\kappa$  scores of 0.788 (SE=0.095) and 0.707 (SE=0.095) for agreement of physical and mental health, respectively.<sup>21</sup>

The MOS-HIV and SF-12v2 are normalized to the 1998 United States population with a mean value of 50 and a standard deviation of 10.<sup>13,14,20</sup> In a comparative review by Clayson et al.<sup>15</sup> the MOS-HIV was identified as one of the preferred disease-targeted measures since it is brief and practical to administer, the input of people living with HIV/AIDS was used in its development, there is well established evidence for reliability, validity and responsiveness and it has been successfully used in clinical trials.

Interpretation of HRQoL scores can be a difficult task, in fact, some authors project that more data are needed to aid interpretation of what HRQoL scores mean.<sup>3</sup> For the purposes of this statistical analysis, differences in HRQoL will be interpreted using effect size, which represents a standardized measure of change in a group or a difference

in changes between two groups.<sup>22</sup> Effect size is recommended to assess the magnitude and meaning of health status changes, and is often expressed in standard deviation units.<sup>14,22</sup> Because there is no widely accepted notion of what constitutes a clinically meaningful change in health status and because researchers and clinicians alike do not yet have enough experience to apply a raw score on a health status scale clinically, effect size can be used as a specific benchmark or standard for interpreting health status. Effect-size benchmarks have been established at a general level to guide interpretation of the relative magnitude of change of a HRQoL measure.<sup>22</sup> Cohen defined, in standard deviation units, an effect size of 0.2 as a small difference, an effect size of 0.5 as a moderate difference and an effect size of 0.8 as a large difference in HRQoL between groups, representing a difference of at least four-fifths of a standard deviation of the comparison measure.<sup>14,23</sup> Wu et al. also points out that a difference or change of 1.0 standard deviation units will almost always be a meaningful.<sup>14</sup>

#### ***1.4 HRQoL in the context of HIV infection***

People living with HIV/AIDS generally have lower physical and mental HRQoL scores when compared to the general population. A cross-sectional questionnaire-based study conducted by Miners et al. found that HIV positive men and women in the United Kingdom scored lower on all five domains on the EQ-5D quality of life measure including mobility, self-care, usual activities, pain/discomfort and anxiety/depression irrespective of similarities in age and gender. Univariable and subsequent multivariable regression analysis demonstrated that people living with HIV infection had significantly lower utility and visual analogue scale scores on the EQ-5D compared with the general

population; HIV infection independently decreased the utility and visual analogue scale scores of the EQ-5D by 20%.<sup>24</sup>

Researchers have compared the HRQoL of people co-infected with more than one chronic, viral infection to those singly infected or with the general population in order to understand the influence of a chronic, viral infection on HRQoL. Mrus and colleagues assessed health values of people living with HIV and Hepatitis C (HCV) co-infection and compared them with those singly infected with HIV or HCV and the general population. They found that individuals with HIV, HCV or HIV/HCV co-infection had lower HRQoL summary scores as measured by the SF-12 compared to United States national norms.<sup>25</sup> People who were co-infected with HIV and HCV had significantly more depressive symptoms, less social support and lower self-esteem scores compared to those living with HCV alone. The authors attributed this to differences in demographic characteristics between groups where the HCV mono-infected group was comprised of more white, heterosexual, highly educated and employed individuals.<sup>25</sup> As highlighted in the study by Mrus et al., there are a multitude of reasons why people living with HIV typically may have worse perceived HRQoL compared to the general population, which will be explored further herein.

#### *1.4.1 Determinants of health and living with HIV*

Many HIV-positive men and women are challenged by social and economic factors that can negatively affect their health and well-being. Kass et al.<sup>26</sup> found that living with HIV was associated with a loss of employment and income, and a study of families affected by HIV/AIDS conducted by Goldie et al. found that over half of parents

reported a family income of less than \$20,000 and 87% reported an annual income of \$30,000 or less.<sup>27</sup> In a report commissioned by the Public Health Agency of Canada, social determinants of health, for example, poverty, lack of affordable housing, racism, stigma and discrimination were found to be associated with one's vulnerability to HIV infection, the rate of progression to AIDS and a person's ability to manage with the disease.<sup>28</sup>

#### *1.4.2. HIV infection in women*

There are an increasing number of women becoming infected with HIV/AIDS. By 2006, the proportion of positive HIV test reports attributed to females of all ages had reached 27.8%, the highest percentage since the start of the epidemic, compared to 11.7% prior to 1999.<sup>29</sup> Surveillance data published by the Public Health Agency of Canada for 2008 demonstrated that 26.2% of all positive tests were among females, an increase of 11.2% compared to the previous year. Women also accounted for the majority (58.3%) of all positive test reports among young adults aged 15 to 19 years, which was a noted trend for the last 10 years of surveillance data.<sup>29</sup>

Women living with HIV may experience the intersection of multiple oppressions and health-related challenges. Not only may women experience challenges related to accessing health care, stigma and discrimination, sub-optimal housing conditions, conflict with family services and financial strain, but also issues around gender inequity, power dynamics in social and sexual relationships as well as economic and social oppression.

The British Columbia Positive Women's Survey was conducted between 1994 and 1996 in order to better understand how sociodemographic characteristics are related

to risk factors for HIV infection, HIV testing experiences, health status and degree of satisfaction with medical care. Psychosocial problems identified by the 110 HIV-positive female participants as the most frequent were financial strain, lack of intimacy or satisfying sexual relationships, fear of rejection or discrimination and lack of affordable housing.<sup>30</sup>

HIV-positive women may have a lower mental HRQoL as measured by the MOS-HIV when compared to HIV-positive men. In multivariable stepwise regression analysis, Miners et al. demonstrated that the MOS-HIV MHS was strongly associated with gender ( $p=0.004$ ); females had significantly lower MHS scores than males.<sup>24</sup> Although the trend was similar in univariable analysis, the difference was not statistically significant ( $\beta=-6.50$ ,  $p=0.08$ ).<sup>24</sup> The PHS of the MOS-HIV was also significantly lower in HIV-positive women compared to HIV-positive men in univariable analysis ( $\beta=-7.79$ ,  $p=0.04$ ), but this trend was not significant in multivariable regression.<sup>24</sup> Although this study presents some evidence of a potential association between HRQoL and gender as well as a difference in HRQoL between HIV-positive men and women, these results must be interpreted with caution as 89% of the cohort was male and 45% cited sex with other men as a risk factor for HIV acquisition. There may be other contextual factors not captured in this analysis that are confounding this association and need to be explored further.

Individuals in lower socioeconomic classes bear a disproportionate amount of both acute and chronic stressful experiences, are more vulnerable to the negative effects of stress and have fewer and less effective resources available to address their challenges.<sup>31</sup> Given that women are generally more socioeconomically disadvantaged than men, one may conclude that women may experience more stressful events and be

more vulnerable to experiencing negative effects compared to men. Given the different social, political, and economic roles that women play in society, women may be exposed to different types of stress compared to men, all of which could impact their perceived HRQoL.<sup>27,32</sup>

#### *1.4.3. Mental illness in HIV*

Depression is a common mental illness in the medically ill exceeding the prevalence found in the general population.<sup>33,34</sup> In the general population, the lifetime prevalence of depressive disorders in women is almost twice that in men, irrespective of chronic illnesses including HIV/AIDS.<sup>187</sup> The one-year prevalence of major depression varies in people living with HIV/AIDS from 1.9% to 35% in a clinical context and from 30% to 60% in a community context.<sup>35,36</sup> The lifetime prevalence of depression in people living with HIV/AIDS has been estimated at 20-45%;<sup>37-41</sup> and it is estimated that 60% of people living with HIV in Ontario may suffer from depression.<sup>42,43</sup> Studies conducted in the United States have demonstrated a difference in prevalence by gender with approximately 30 to 40% of HIV-positive men and 40 to 60% of HIV-positive women experiencing significant depression.<sup>39,44,45</sup> Psychological stress plays an important role in the development of depressive symptoms<sup>46</sup> and women are especially at risk for psychological distress and depression.<sup>47,48</sup>

Depression is associated with poor health, greater health service utilization, and poor quality of life and social support, which may manifest into poor adherence to HIV medication<sup>38,41,42</sup> and HIV disease progression.<sup>49</sup> Several factors have been identified that may predict increased depression in people living with HIV including number of years



living with HIV, avoidant *versus* active coping style, excessive rumination about health-related problems, past history of depression, personality disorders, and low levels of social support.<sup>24,30,39,50-52</sup> In a cross-sectional analysis of data collected as part of a longitudinal cohort study investigating neuropsychiatric, psychosocial, neuroendocrine, and immune aspects of HIV infection in women, the rate of current major depressive disorder was four times higher in HIV-positive women (19.4%) versus HIV-negative women (4.8%); major depressive disorder was diagnosed via the Structured Clinical Interview for DSM-IV.<sup>36</sup> Also, HIV-positive women had significantly higher depressive symptom scores on the Hamilton Depression Rating Scale relative to HIV-negative women.<sup>36</sup>

Anxiety disorders are the most common type of mental illness in the general population; all combined anxiety disorders including generalized anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder and social phobias affect approximately 12% of Canadians, or about 9% of men and 16% of women.<sup>53,54</sup> Few studies have been published describing the prevalence of anxiety disorders in HIV-positive individuals, especially HIV-positive women.<sup>36,55</sup> Goggin et al. found that 1.9% of HIV-positive women had generalized anxiety disorder.<sup>55</sup> Morrison et al. also found that, relative to HIV-negative women, HIV-positive women had higher levels of anxiety symptoms as measured by the Hamilton Anxiety Rating Scale (HIV-positive women mean score: 8.8, SD=8.9; HIV-negative women mean score: 3.6, SD= 5.5;  $p<0.0001$ ).<sup>36</sup> Despite this observation, the proportion of women with anxiety disorders diagnosed by the Structured Clinical Interview for DSM-IV was not significantly different between

HIV-positive and HIV-negative women (10.8% for HIV-positive vs. 6.5% for HIV-negative women).<sup>36</sup>

Substance use disorder is also highly prevalent among HIV-positive men and women<sup>56,57</sup>; and is known to negatively impact adherence to antiretroviral medication and perceived HRQoL of people living with HIV. A study by Korthuis et al.<sup>56</sup> found that mental HRQoL was reduced for current drug users and that all illicit drugs were associated with decreased mental HRQoL including marijuana, non-prescription analgesics, cocaine and inhalants. Similarly, using multivariable linear regression, Ion et al. demonstrated that current and former cigarette smoking and a history of drug use (including marijuana, cocaine and heroin) were negatively associated with the PHS of the MOS-HIV and SF-12v2.<sup>58</sup>

#### *1.4.4. Relationship between biological surrogates of HIV infection and HRQoL*

CD4 lymphocyte count and HIV viral load, that is, the number of HIV RNA copies per ml of plasma, have served as proxy or biological surrogate markers of the degree of immunosuppression and HIV disease progression.<sup>59-61</sup> Research in both the pre and post-HAART eras has been conducted in order to explore how changes in HIV disease status over time as measured by CD4 cell count and HIV viral load may correspond with changes in perceived health status or HRQoL. The results of these studies have been mixed resulting in an unclear understanding of the association between measures of immunosuppression or HIV disease progression and HRQoL. Pre-HAART investigations have reported moderate, but statistically significant correlations between HRQoL summary scores and sub-domains with numerous indices of disease status

including CD4 cell count, time since HIV diagnosis, number of HIV-related illnesses, etc.<sup>17,62,63</sup> Some studies conducted in the post-HAART era have found no statistically significant association between CD4 cell count and any HRQoL dimensions or summary scores,<sup>19,24,64,65</sup> whereas others have reported an association between the degree of immunosuppression and patient-reported HRQoL.<sup>66,67</sup> Weinfurt et al.<sup>66</sup> found that different measures of HIV viral load including baseline viral load, early response to treatment and weekly change, as well as CD4 lymphocyte count were all significantly related to changes in the PHS and MHS of the MOS-HIV. This randomized controlled trial investigating antiretroviral therapy found that lower baseline viral load and increasing CD4 count were associated with improvements in HRQoL over time. These results should be considered with the caveat that although participants and the treating physician were blind to the plasma viral load at the time of HRQoL questionnaire completion, at each study visit participants were aware of their CD4 count, which may have affected how they were completing the MOS-HIV HRQoL instrument. A cross-sectional, multivariable analysis conducted by Gill et al.<sup>67</sup> found that individuals with CD4 counts less than 200 cells had significantly lower physical functioning, role function and general health perceptions compared to those with CD4 counts greater than 500 cells; and in comparison to those with an undetectable viral load, individuals with viral loads ranging from  $\log_{10}2.6$  to  $\log_{10}4.0$  had lower physical functioning scores. Aside from measures of immunosuppression and disease progression, there may be other clinical factors or co-morbid health conditions that are associated with physical and mental HRQoL in the context of HIV infection. In the next section, the epidemiology and

clinical importance of a specific co-morbid health condition that is relevant to HIV infection, namely herpes simplex virus type 2, will be discussed.

### ***1.5 HSV-2 infection in HIV populations***

Herpes simplex virus type 2 (HSV-2) is one of the most prevalent sexually transmitted infections and is the most common causes of genital ulcers worldwide.<sup>68-71</sup> The life-time prevalence of HSV-2 is higher in people infected with HIV ranging from 30% to 70% in the United States, Canada and Europe and 50% to 90% in Africa.<sup>68-79</sup> Romanowski and colleagues<sup>77</sup> recently published HSV-2 sero-prevalence data in an HIV population across three Canadian cities including Edmonton, Toronto and Quebec City. In this cross-sectional analysis of 629 HIV-positive men and women, HSV-2 seroprevalence was 54.6%. Compared to men, women were 2.7 times (95% CI: 1.8-3.9) more likely to be sero-positive for HSV-2. Non-Canadian-born participants were 2.0 times (95% CI: 1.4-3.0) more likely, and participants who described themselves as non-white were 3.2 times (95% CI: 2.2-4.5) more likely, to be HSV-2 sero-positive. These findings were similar to Ramaswamy et al.<sup>74</sup> who investigated HSV-2 seroprevalence at HIV diagnosis. This cross-sectional analysis consisted of 850 adult men and women diagnosed with HIV between 1986 and 2001 in the United Kingdom. HSV-2 seroprevalence was 63% (95% CI 60-66%); and was associated with heterosexual risk group, black ethnicity, older age and female gender. In fact, 76% of women aged 17 to 66 were HSV-2 sero-positive compared to 56% of men aged 17 to 71 included in the analysis (p=0.0001). Results of the univariable analysis suggested that there was an association between HSV-2 seropositivity and female gender, heterosexuality and black-

African or black-Caribbean ethnicity. Because most of the heterosexual individuals included in the analysis were women, the authors identified a possible confounding relationship between gender and risk factor for HIV acquisition, which was explored via multivariable logistic regression. In multivariable regression analysis, HSV-2 seropositivity remained strongly associated with black ethnicity and older age at the time of HIV diagnosis. After controlling for these variables, the model revealed that black-African women were 3.25 times more likely to be HSV-2 sero-positive at HIV diagnosis (95% CI 2.25-4.71,  $p=0.0001$ ) compared to black-African men.<sup>74</sup>

Other risk factors for HSV-2 seropositivity in HIV-positive women have been cited in the literature including a history of sexually transmitted infections, a history of sex work, number of years of sexual activity and earlier sexual debut, non-White ethnicity (for example, African-American or Latina/Hispanic race), a low household income (for example, less than \$18,000 USD) and less education (for example, less than 12 years).<sup>72,79</sup>

Many individuals who are infected with HSV-2, even if co-infected with HIV, are not aware of their status. Romanowski et al. reported that only 30.3% of the men and women co-infected with HIV and HSV-2 reported a history of genital herpes, suggesting that the majority of people in this cross-sectional analysis who were living with HSV-2 infection were asymptomatic.<sup>77</sup> Similarly, only 22 (10%) of the 223 HSV-2/HIV co-infected outpatients followed prospectively in a French cohort study had a clinical history of genital herpes at the time of inclusion or within the 12-month period before study enrollment.<sup>78</sup> The majority of HSV-2 positive participants (69%) were totally unaware of

their genital herpes infection at study enrollment whereas the remaining 47 patients (21%) were aware of their HSV-2 status by a history of past genital herpes outbreaks.<sup>78</sup>

Observational epidemiological and biological studies have suggested that there is a synergistic link between HIV and HSV-2 infections whereby HSV-2 facilitates acquisition and transmission of HIV and is involved in HIV disease progression in co-infected individuals.<sup>80-88</sup>

In a systematic review and meta-analysis of 18 longitudinal studies, Freeman et al. found that prevalent HSV-2 infection was a statistically significant risk factor for HIV acquisition in both men (adjusted RR, 2.7; 95% CI, 1.9-3.9) and women (adjusted RR, 3.1; 95% CI, 1.7-5.6) in the general population. The meta-analysis adjusted for age and sexual behaviour, which were considered a priori confounders of the relationship between HSV-2 seropositivity and subsequent infection with HIV.<sup>85</sup> It is thought that HSV-2 facilitates HIV acquisition at the molecular level causing mucosal disruption at the epithelial surface and subsequent recruitment of activated CD4 lymphocytes to the area, increasing susceptibility to HIV infection.<sup>83,84,89,90</sup> In HIV and HSV-2 co-infection, *in vivo* and *in vitro* studies have demonstrated that HSV-2 facilitates shedding and transmission of HIV. When HIV-infected CD4 T lymphocytes are recruited to herpetic lesions, HSV regulatory proteins including ICP0, ICP4 and VP16 upregulate HIV replication, thereby increasing the frequency and titer of mucosal HIV shedding.<sup>83,91-94</sup>

Studies have further described how the upregulation of HIV replication by HSV regulatory proteins may influence HIV viral loads in co-infected individuals, however, the results of these studies have been mixed. For example, LeGoff et al.<sup>95</sup> investigated clinical correlates of HSV-2 DNA and HIV RNA among women with genital ulcer

disease who were participating in a randomized controlled trial of episodic herpes treatment in Ghana and the Central African Republic. This cross-sectional analysis found that, compared to HIV-positive women without genital (cervicovaginal or lesional) HSV-2 infection, women with genital HSV-2 DNA were significantly more likely to have detectable HIV RNA in cervicovaginal lavage (68.3 vs. 42.4%;  $p=0.001$ ) and a higher median cervicovaginal HIV RNA level ( $3.14 \log_{10}$  copies/ml vs.  $2.10 \log_{10}$  copies/ml;  $p=0.003$ ). Furthermore, LeGoff<sup>95</sup> and colleagues found that women with genital HSV-2 DNA had significantly higher plasma HIV RNA levels (median  $5.10 \log_{10}$  copies/ml vs.  $4.65 \log_{10}$  copies/ml;  $p=0.07$ ) and lower CD4 cell counts (median 198 vs. 409 cells/ $\mu$ l;  $p=0.03$ ). Similarly, in a cross-sectional, multivariable analysis of 339 people living with HIV in Uganda, Duffus et al.<sup>96</sup> found that HSV-2 co-infection was associated with a 0.3 log copies/ml higher mean log HIV viral load ( $4.6 \pm 0.94$  vs.  $4.3 \pm 0.91$  log copies/ml,  $p=0.014$ ), but there was not a significant difference in CD4 cell count between co-infected and those without HSV-2 infection. Serwadda et al. also demonstrated in a nested case-control study conducted in Uganda that HSV-2 was associated with a 0.5 log increase in HIV viral load both in early HIV infection (i.e. 5 to 15 months after sero-conversion) and chronic HIV infection.<sup>86</sup> A retrospective cohort study of 294 antiretroviral-naïve, HIV positive men conducted by Cachay et al.<sup>97</sup> compared the baseline and longitudinal plasma HIV viral loads of HSV-2 sero-negative and HSV-2 sero-positive men, the results of which conflicted with the results of the cross-sectional analyses of LeGoff et al. and Duffus et al., as well as the nested case-control study by Serwadda et al. Cachay et al.<sup>97</sup> found that HSV-2 infection had minimal influence on the dynamics of HIV during acute and early infection; HSV-2 seropositive and HSV-2

seronegative groups had similar baseline HIV viral loads during acute infection (5.52 vs. 5.72 log<sub>10</sub> copies/ml; p=0.39) and early infection (4.57 vs. 4.67 log<sub>10</sub> copies/ml; p=0.5). In a longitudinal analysis, the difference in HIV viral loads between HSV-2 sero-positive and HSV-2 sero-negative HIV-positive men remained close to 0 during the first year of infection. The authors accounted for their contrasting results to other studies that have found an association between HIV/HSV-2 co-infection and increased HIV viral load, including the Ugandan Rakai cohort explored in Serwadda et al.,<sup>86</sup> Cachay et al.<sup>97</sup> attributed the contrasting results to differences in sex, ethnicity, nutritional status, additional co-infections and HIV sub-type between the cohorts and argued that the co-existence of endemic diseases including malaria and tuberculosis may have contributed to the higher HIV viral loads. Although studies that have explored the relationship between HSV-2 infection and HIV viral load progression have been mixed, the results of these studies should not be ignored. Clearly additional research is needed in order to understand specifically how HSV-2 facilitates HIV replication and influences the level of cervicovaginal and plasma HIV viral loads, as well as what other contextual or confounding factors may be associated with this relationship. Perhaps new observational studies that are more methodologically rigorous than what has been employed to date, i.e. prospective cohort studies rather than cross-sectional or retrospective cohort studies, would help to understand the relationship between HSV-2 infection and cervicovaginal and plasma HIV viral loads.<sup>98,99</sup> Although prospective cohort studies can be costly and require a larger sample size and longer follow-up time compared to other observational study designs, they can inform directionality and temporality of causation, which is important in understanding the clinical connection between HSV-2 infection and HIV



viral load.<sup>99</sup> For example, one longitudinal study by Nagot et al.<sup>100</sup> demonstrated the importance of both clinical and sub-clinical HSV-2 reactivation in HIV replication. This study found that women co-infected with HIV and HSV-2 who were moderately immunosuppressed and not on antiretroviral therapy for HIV had clinical or sub-clinical HSV-2 reactivations that were associated with a detection of HIV genital shedding during a greater percentage of clinic visits and greater genital and plasma HIV viral loads (i.e.  $+0.5 \log^{10}$  copies/ml).<sup>100</sup> This is one of few longitudinal studies that have reported a relationship between the frequency of HIV RNA detection and levels of genital and plasma HIV RNA detected with the presence of clinical and sub-clinical HSV-2 reactivations.

Similar to the relationship between HSV-2 infection and HIV replication as measured by HIV viral load, some research has demonstrated that the natural history and progression of HSV-2 infection is altered in individuals co-infected with HIV and HSV-2. Co-infected individuals experience more frequent and prolonged sub-clinical reactivation and clinical genital herpes outbreaks compared to those infected with HSV-2 alone.<sup>82,100-102</sup> In a prospective cohort study of 217 HIV-positive women, Wright et al.<sup>101</sup> found that increased frequency of culture-positive HSV-2 genital herpes outbreaks was strongly associated with more advanced HIV-induced immunosuppression, as manifested by lower absolute CD4 T lymphocyte counts ( $p < 0.001$ ) and higher plasma HIV RNA levels ( $p = 0.019$ ). Although some gaps in the literature exist regarding how HSV-2 facilitates shedding and transmission of HIV, as well as how HIV changes the natural progression of HSV-2, there is clearly a biological and epidemiological synergy between these two chronic, sexually transmitted viral infections.

Because of the synergistic relationship between HSV-2 and HIV, there has been increasing interest in investigating how episodic or suppressive treatment for HSV-2 infection may mitigate plasma and genital HIV replication and disease progression. A number of studies have explored the hypothesis that treatment for HSV-2 may delay the time to requiring antiretroviral therapy for HIV by reducing plasma and genital HIV viral loads, potentially preventing HIV transmission in sero-discordant couples. In a randomized, double-blind, placebo-controlled trial of 140 HAART-naïve women co-infected with HIV and HSV-2 from Burkino Faso, Nagot et al. found that 12 weeks of HSV suppressive therapy with valacyclovir 500 mg twice daily was associated with a significant decrease in the frequency of genital HIV RNA (OR 0.41, 95% CI - 0.21, 0.80), and the mean quantity of genital HIV RNA was significantly lower in those taking valacyclovir compared to placebo. Similarly, the mean plasma HIV viral load was significantly lower in the valacyclovir group compared to placebo (reduction of 0.53  $\log_{10}$  copies/ml, 95% CI - 0.72, -0.35) after adjusting for the mean baseline phase value.<sup>103</sup> The treatment effect of valacyclovir on plasma and genital HIV RNA increased over the 3-month follow-up period, suggesting that a longer duration of treatment may have resulted in an even greater reduction in HIV RNA levels. Similarly, Baeten et al. conducted a randomized cross-over trial of 8 weeks of suppressive valacyclovir at 500 mg twice daily in 20 Peruvian HAART-naïve women co-infected with HIV and HSV-2. This trial found that the plasma HIV viral load was 45% lower during the valacyclovir arm compared to the placebo arm (reduction of 0.26  $\log_{10}$  copies/ml, 95% CI -0.33, -0.19,  $p < 0.001$ ), and the cervical HIV viral load was 55% lower in the valacyclovir group compared to placebo (reduction of 0.35  $\log_{10}$  copies/ml, 95% CI -0.46, -0.25),

$p < 0.001$ ).<sup>104</sup> The authors suggested that although HSV-2 suppression with daily valacyclovir reduced plasma and genital HIV viral loads in moderately immunosuppressed, co-infected women not requiring HAART, and that the role of suppressive HSV-2 therapy on HIV transmission was yet to be determined, plasma and genital HIV viral loads may have offered surrogate marker evidence that HSV suppressive therapy could reduce HIV infectiousness and slow down HIV disease progression.<sup>104</sup> In a more recent, large-scale randomized, placebo-controlled trial involving 14 sites in southern Africa and east Africa and a sample size of 3381 HAART-naïve heterosexual men and women co-infected with HIV and HSV-2, Lingappa et al. sought to explore whether 24 months of suppressive acyclovir for HSV-2 delayed HIV disease progression.<sup>105</sup> Effect of acyclovir on HIV disease progression was defined by a primary composite endpoint of first occurrence of CD4 cell count of fewer than 200 cells/ $\mu$ l, antiretroviral therapy initiation, or non-trauma related death. This study found that 400 mg of acyclovir twice daily moderately reduced the risk of HIV disease progression by 16% (HR 0.84, 95% CI 0.71, 0.98,  $p=0.03$ ). In those participants with CD4 T lymphocyte counts of  $\geq 350$  cells per  $\mu$ l, acyclovir delayed risk of CD4 cell counts falling below 350 cells/ $\mu$ l by 19% (HR 0.81, 95% CI 0.71, 0.93,  $p=0.002$ ).

The role of suppressive therapy for HSV-2 is currently being investigated in a Canadian context; the CIHR Canadian HIV Trials Network is currently enrolling participants into a multi-centre, randomized, placebo-controlled trial across 24 sites in Canada and Brazil.<sup>106</sup> VALIDATE, or Valacyclovir In Delaying Antiretroviral Treatment Entry, aims to examine whether oral valacyclovir 500mg twice daily can slow the rate of CD4 count decline and ultimately delay the need to start HAART in HIV and

HSV-2 co-infected adults with infrequent recurrences of herpes who do not currently need nor take HAART.<sup>106</sup>

Most studies exploring the relationship between HSV therapy and HIV disease progression have been interested in suppressive treatment, however, one randomized, placebo-controlled trial by Mayaud et al. sought to explore the influence of episodic acyclovir on HIV disease.<sup>107</sup> Women from Ghana and the Central African Republic who had genital ulcers were randomized and followed for 28 days. Episodic acyclovir was effective at reducing cervicovaginal HSV-2 viral load and healing genital herpes ulcers, however, it was not effective at reducing the mean quantity of cervicovaginal HIV viral load among women with detectable cervicovaginal HIV RNA at day 7 (reduction of 0.06 log<sub>10</sub> copies/ml, 95% CI -0.4, 0.3), or reducing plasma HIV viral loads after 14 (increase of 0.09 log<sub>10</sub> copies/ml, 95% -0.1, 0.3) and 28 (increase in 0.01 log<sub>10</sub> copies/ml, 95% -0.3, 0.4) days of treatment.<sup>107</sup>

The long-term effect of HSV suppressive therapy on HIV disease progression is not yet known and continues to be studied in randomized controlled trials. Tanton et al. recently completed a randomized, placebo-controlled trial of 400 mg of acyclovir twice daily in order to determine the effect of 24 months of HSV suppressive therapy on genital and plasma HIV RNA.<sup>108</sup> This study enrolled 484 HIV and HSV-2 co-infected Tanzanian women; the primary outcomes were detection and quantity of cervicovaginal HIV viral load at 6 months. There was little evidence of an effect of acyclovir on detection or quantity of cervicovaginal HIV or HSV-2 viral loads or plasma HIV viral load after 6, 12 and 24 months of treatment, which contrasts with previous trials aforementioned that found substantial reductions in genital and plasma HIV viral loads after 3 months of

treatment.<sup>108</sup> The authors attributed the difference between their trial results and previous trial findings to a combination of sub-optimal adherence during the 24 months of follow-up and the regimen used, citing valacyclovir as a more appropriate choice because of increased oral bioavailability and higher trough plasma concentrations compared to acyclovir. Tanton et al. concluded that acyclovir 400 mg twice daily was unlikely an useful long-term intervention to reduce plasma HIV viral loads and prevent HIV transmission, especially in transient populations where it may be difficult to achieve optimal adherence for HSV-2 suppression.<sup>108</sup> Similarly, Celum et al. investigated whether therapy to suppress HSV-2 reduced transmission of HIV because it was known to reduce the frequency of reactivation of HSV-2, as well as genital and plasma HIV levels.<sup>109</sup> A total of 3408 serodiscordant couples, of whom the HIV-positive partner was not taking antiretroviral therapy at the time of enrollment and had a CD4 count of at least 250 cells, were included in this randomized, placebo-controlled trial of acyclovir 400 mg twice daily. The primary outcome of interest was transmission of HIV to the partner who was not initially infected with HIV after 24 months of follow-up. The authors found that although suppressive acyclovir reduced plasma HIV viral load by 0.25 log<sub>10</sub> copies per ml and reduced occurrence of genital herpes ulcers by 73%, the risk of transmission of HIV was not reduced. Of the 84 linked transmissions included in the analysis, or those classified as likely to have been acquired from the person's study partner, 41 occurred in the acyclovir group and 43 in the placebo group (HR with acyclovir, 0.92; 95% CI, 0.60 to 1.41; p=0.69).<sup>109</sup>

A number of studies have investigated the relationship between HSV-2 suppressive therapy and HIV disease progression, and many support the claim that

suppressive therapy reduces plasma and genital levels of HIV and may effect rate of CD4 cell count decline.<sup>103-105</sup> What is less promising is the role that suppressive HSV-2 therapy may play in averting HIV transmission.<sup>109,110</sup> No studies have explored to what extent HSV-2 infection complicates ones ability to manage living with HIV, and how HSV-2 infection may affect well-being and perceived HRQoL when coupled with HIV.

For many people, the psychological impact of having symptomatic genital herpes overshadows the physical morbidity associated with it. In the 1980s and 1990s there was much interest in investigating the psychological issues relating to living with genital herpes, but this has not been explored in the context of co-infection with HIV. Patel et al<sup>111</sup> studied patient perspectives about the burden of recurrent genital herpes in HIV-negative men and women who had had at least two herpes episodes in the previous year and had not received suppressive anti-viral therapy for HSV-2. Triggers for herpes recurrence reported by participants were mental stress (73%), friction of genital skin (48%), lack of sleep (47%) and physical stress (45%). Mental health as measured by the Recurrent Genital Herpes Quality of Life questionnaire was significantly lower in the study population with recurrent genital herpes. Recurrence frequency, severity of pain, and previous experience with suppressive therapy had a significant impact on both the PHS and MHS and HRQoL dimensions measured with the largest differences observed for the dimensions Role Emotional, Social Functioning and Mental Health. Similarly, Goldmeier et al. found that individuals with recurrent genital herpes were more psychologically distressed compared to those experiencing their first herpes attack as measured by the General Health Questionnaire.<sup>112</sup> These studies suggest that individuals with recurrent genital herpes may have a higher prevalence of symptoms of psychiatric

disorders, most notably symptoms of anxiety and depression, compared to those without recurrent genital herpes and those experiencing their first outbreak. The prevalence of anxiety and depression disorders may be even higher in a group of HIV-positive individuals with recurrent genital herpes because of the relationship between anxiety, depression and both viral infections.

Living with genital herpes can also have psychosexual implications. Shaw et al. demonstrated that women with recurrent genital herpes experienced significantly greater sexual dissatisfaction than women with curable sexually transmitted infections (STIs) and those with no history of STIs;<sup>113</sup> however the study groups did not differ with regard to symptoms of depression, anxiety, somatic preoccupation and social withdrawal and these women were not co-infected with HIV. Green and colleagues found that people with recurrent genital herpes experienced a range of psychological problems including fear of transmitting the virus to others, fear of possible long-term consequences for general health, problems with intimacy and spontaneity, and feelings of undesirability.<sup>114</sup> Bickford et al. further explored the relationship between psychosexual factors and genital herpes incorporating issues of stigma, anxiety and disclosure and how herpes stigma can complicate the course of sexual relationships and disclosure within those relationships.<sup>115</sup> Finally, Luby and colleagues explored the impact of genital herpes on HIV-negative men and women on a variety of life factors including socialization, work enjoyment and performance, self-image, sexual attitudes and behaviours and psychological states.<sup>116</sup> Herpes did not interfere greatly with work performance or relationships with colleagues; slightly greater but still moderate interference was reported for work satisfaction and

enjoyment. Herpes interfered most with enjoyment in meeting persons of the opposite sex, sexual freedom, frequency and spontaneity.

There is a gap in the literature exploring the relationship between genital herpes recurrence, stress and anxiety in HIV-positive women. One study by Pereira et al.<sup>117</sup> found that life stress, particularly stress that was recent, was strongly associated with recurrence of genital herpes in HIV-positive women.

Little is known about the experiences of women living with these two chronic sexually transmitted viral infections. It is not known if and how HSV-2 and HIV co-infection complicates the experience of women living with HIV, in particular, how symptomatic HSV-2 infection influences HRQoL compared to HIV-positive women who are not infected with HSV-2 or are HSV-2 positive, but asymptomatic. The degree to which also having symptomatic HSV-2 infection changes perceived physical and mental health of HIV-positive women when taking into account other factors related to HRQoL including the degree of immunosuppression (for example, CD4 count), demographic characteristics (for example, ethnicity and socioeconomic status) and co-existent psychological issues (for example, symptoms of depression and anxiety) is not known. It has not been investigated whether if and how living with two chronic, sexually transmitted viral infections including symptomatic HSV-2 creates additional challenges in social and sexual relationships for women, how issues regarding body image and self-esteem are complicated or how women perceive and experience stigma and discrimination, especially around disclosure in relationships. It is not understood how HIV-positive women experience genital herpes within their broader social location and historical context, that is, if and to what extent these women's lives are complicated when



different forms of oppression and marginalization including gender, race and socioeconomic status intersect. No quantitative or qualitative studies have explored any of these phenomena in a Canadian HIV-positive female population.

### ***1.6 Impact of treatment for HIV and HSV-2 on HRQoL***

In trying to understand how symptomatic HSV-2 infection is associated with HRQoL of HIV-positive women, it is important to consider receipt of both HAART for HIV and / or suppressive anti-viral therapy for HSV-2, as these treatments have been positively associated with HRQoL. A systematic review recently completed by Ion et al.<sup>118</sup> showed that HAART improved both long-term physical and mental HRQoL of treatment-naïve, HIV-positive adult men and women compared to pre-HAART HRQoL. Both the PHS and MHS of the MOS-HIV increased gradually over time after initiation of HAART with the most dramatic increase was observed within 52 weeks of starting treatment. Sub-group analyses effectively demonstrated further differences in the impact of HAART on HRQoL of people living with HIV depending on the type of regimen they were receiving (i.e. NNRTI-based versus PI-based regimens) and where geographically they were accessing HAART.

There is also evidence that receipt of suppressive anti-viral therapy for recurrent genital herpes is positively associated with HRQoL. Patel et al investigated the potential benefits of suppressive antiviral therapy on HRQoL in an international, multi-centre, randomized, double blind, placebo-controlled, parallel group study of once and twice daily valacyclovir and acyclovir for recurrent genital herpes in people without HIV infection.<sup>119</sup> HRQoL was measured by the Recurrent Genital Herpes Quality of Life

Questionnaire and statistical significance of a treatment-related change in HRQoL score from baseline for each active treatment group in comparison to placebo was tested at 3, 6 and 12 months using analysis of variance. Changes in HRQoL scores from baseline were significantly greater in the active treatment groups than in the placebo group after 3, 6 and 12 months. Also, a sustained beneficial impact of HSV treatments was observed across all treatment regimens with no significant differences in HRQoL score between treatment groups.<sup>119</sup> Carney et al also demonstrated in an HIV-negative population that although a higher proportion of people living with genital herpes had increased psychiatric morbidity compared to people without genital herpes, receipt of suppressive acyclovir for genital herpes resulted in a significant decrease in the proportion of people with symptoms of anxiety and illness concern.<sup>120</sup> It is not known if or how receipt of HAART or suppressive therapy for recurrent genital herpes may change perception of stressors that HIV and HSV-2 co-infected women experience, thereby affecting their perceived physical and mental HRQoL.

The overall purpose of this study was to explore the quantitative and qualitative relationships between HIV and symptomatic HSV-2 co-infection and the physical and mental HRQoL of HIV-positive adult women. This exploratory analysis was conducted while taking into account other confounding and/or contextual factors that may influence HRQoL including co-morbid symptoms of mental illness such as depression and anxiety, biological surrogates such as CD4 cell count, ethnicity and receipt of treatment for HIV and HSV-2.

## **1.7 Proposed methodology**

### ***1.7.1 Need for a mixed methods approach***

Mixed methods can be used when neither quantitative nor qualitative components alone can provide a comprehensive overview and understanding of the phenomenon in question.<sup>121,122</sup> Mixed methods are increasingly being used to recognize the complexity of human lives which are often embedded within rich and intricate contexts.<sup>122</sup> A mixed methods approach is ideal for this study because of the lack of qualitative and quantitative evidence regarding if and how HSV-2 and HIV co-infection complicates the experience of women living with HIV and, in particular, how symptomatic HSV-2 infection influences the HRQoL of HIV-positive Canadian women. A mixed methods sequential follow-up exploratory approach was used, which involved collecting qualitative data after a quantitative phase. This follow-up exploratory model was chosen to enable a qualitative contextualization of the quantitative statistical relationships explored.<sup>121</sup> The quantitative statistical analysis informed the qualitative interpretive phenomenological approach that was employed to explore in greater depth the experiences of women living with HIV and HSV-2 and the relationship between co-infection and HRQoL.<sup>123,124</sup> A mixed-methods sequential exploratory design was also chosen to ensure complementarity and a comprehensive investigation of HIV and HSV-2 co-infection in adult women.<sup>123</sup> As stated by Greene et al., the goal for complementarity is to “measure overlapping but also different facets of a phenomenon, yielding an enriched, elaborated understanding of that phenomenon.”<sup>125</sup>

### ***1.7.2 Mixed methods purpose statement***

This mixed methods study explored the association between HIV and HSV-2 co-infection and physical and mental HRQoL of adult HIV-positive women. A sequential exploratory model was utilized, which involved collecting qualitative data after a quantitative phase in order to follow-up on and explore the quantitative data in greater depth. In the first quantitative phase, a cross-sectional questionnaire was administered, HSV-2 sero-status was determined and clinical correlates and HRQoL scores were analyzed using multivariable methods. The purpose of the multivariable analysis was to provide a general understanding of the association between HIV and HSV-2 co-infection and HRQoL of adult HIV-positive women. The second qualitative phase was conducted to refine and further explain the quantitative phase by exploring in more depth participants' views of the relationship between symptomatic HSV-2 and HIV co-infection and HRQoL.<sup>123,124</sup> Interpretive phenomenology philosophy and methodology informed the qualitative phase.

### ***1.7.3 Priority of research stages***

In this mixed methods study, the quantitative and qualitative components were given equal priority or weighting throughout the data collection and analysis processes as both phases represented significant aspects of the research objective to understand the association between symptomatic HSV-2 and HIV co-infection and HRQoL.<sup>124</sup> The quantitative component was conducted first providing statistical data on the relationship between HSV-2 and HIV co-infection and HRQoL, and identified issues and outcomes to be explored in the qualitative phase. The qualitative phase explored and interpreted the

statistically significant and clinically relevant results obtained in the quantitative phase in an attempt to comprehensively describe the relationship between symptomatic HSV-2 and HIV co-infection and HRQoL of adult women. Overlap between the conclusions drawn in the quantitative and qualitative phases was expected, however, it was also assumed that both phases would provide different yet equally important information to enhance the understanding of HIV-positive women's experiences.

#### ***1.7.4. Integration of quantitative and qualitative methods***

Quantitative and qualitative approaches overlapped at the study design stage as both quantitative and qualitative research questions were introduced and both phases were grounded in a social constructivist theoretical framework embodied in a transformative paradigm,<sup>126</sup> which will be explained in greater detail in a subsequent section of this thesis. The quantitative and qualitative phases were connected at the intermediate stage of the study when the statistical analysis conducted in the quantitative phase informed the sampling and grounded the data collection protocol in the qualitative phase.<sup>124</sup> Quantitative and qualitative data were explored individually for trends then integrated when interpreting the study findings as a whole through the exploration and description of similar and contrasting results. Results from both the quantitative and qualitative phases were also applied to a health psychology model described in the literature. How, why and to what extent the quantitative and qualitative data converged were explored in the final stages of this project.

## **Chapter 2**

### **Understanding the relationship between HSV-2/HIV co-infection and physical and mental HRQoL summary scores in adult women: a cross-sectional analysis**

#### ***2.1 Research questions***

The quantitative phase sought to answer the following primary and secondary research questions: “Is there a difference in the physical and mental HRQoL of adult women co-infected with HSV-2 and HIV as measured by the MOS-HIV and SF-12v2 compared to adult women who are infected with HIV alone?” and “Is there a difference in the prevalence and severity of anxiety and depression symptoms as measured by the Hospital Anxiety and Depression Scale (HADS) in adult women co-infected with HSV-2 and HIV compared to adult women who are infected with HIV alone?” If a statistically significant difference in anxiety and depression symptomatology between the two groups was observed, the HADS score was to be integrated into the multivariable regression modeling to understand how it may modify or confound the relationship between HSV-2 infection and HRQoL of adult HIV-positive women.

#### ***2.2 Quantitative phase hypotheses***

After review of the literature and in consideration of the primary and secondary research questions proposed, the following hypotheses were presented: (1) Women living with HSV-2 and HIV will have a significantly lower MHS compared to women living with HIV alone; (2) HSV-2/HIV co-infected women will have a similar PHS compared to women living with HIV alone as it is believed that infection with HSV-2 affects women more socially and psychologically than physically; and (3) Women co-infected with HSV-2 and HIV will have a significantly higher prevalence and severity of anxiety and

depression symptoms as measured by the HADS compared to women living with HIV alone due to the presence of HSV-2 itself. The role of anxiety and depression symptomatology as a confounder or effect modifier will be explored through multivariable regression modeling.

### ***2.3 Quantitative methods***

A cohort study exploring Herpesvirus and HIV co-infection was established in Hamilton in 2005 as a partnership between clinicians at the Hamilton Health Sciences Special Immunology Services (SIS) clinic and basic scientists from the McMaster University Centre for Gene Therapeutics. Originally the study was designed in order to measure the overall sero-prevalence of Herpes simplex virus (HSV) types 1 and 2 and cytomegalovirus (CMV), as well as to determine the clinical correlates of Herpesvirus and HIV co-infection including degree of immunosuppression, sociodemographic variables and HRQoL in HIV-positive women accessing care at the SIS clinic. This cohort study has enabled the cross-sectional analysis conducted and discussed herein as part of the quantitative phase of this mixed methods study. The HSV/HIV Co-Infection Study was approved by the Hamilton Health Sciences / Faculty of Health Sciences Research Ethics Board. All participants gave informed consent prior to inclusion in the cohort study and analysis of their data. Informed consent enabled collection of blood for Herpesvirus serology as well as collection of clinical data via medical chart review.

### *2.3.1 Sampling strategy*

HIV-positive women between the ages of 18 and 60 were sampled while attending routine appointments at the SIS clinic approximately every 3 months. Convenience or non-probability sampling was chosen as it was the goal to recruit as many HIV-positive women attending routine clinic appointments as possible during the three-year enrollment period. It was felt that this sampling strategy would achieve representativeness or comparability to the broader female population at the SIS clinic<sup>127</sup> because a large proportion of the entire clinic female patient population would be enrolled. Neither random nor stratified probability sampling were incorporated into the original co-infection study protocol. Random sampling was not feasible for the quantitative phase of this study because of how patient records are maintained electronically and clinic appointments are scheduled at the SIS clinic, for example, there was not a list of all the female patients from which a random or stratified sample could be selected. Women were invited regardless of ethnicities and backgrounds; no exclusions were made on the basis of other medical conditions. Women receiving anti-retroviral therapy as well as women who were HAART-naive were included. Also women receiving no treatment, episodic therapy or suppressive therapy for HSV-2 infection and/or symptomatic genital herpes were included. Women were excluded if they were unable to read, write and correspond in English, as they had to complete self-report questionnaires.



### *2.3.2. Data collection*

#### 2.3.2.1. Measuring exposure to Herpesviruses

HSV-2 sero-status was the primary exposure or clinical correlate of interest. A 20 ml sample of blood was taken during routine blood draw and processed in the research laboratory of Dr. Charu Kaushic. HSV-2 sero-positivity was determined using two laboratory tests: the Focus Diagnostics EIA IgG ELISA and the Focus IgG immunoblot, which was considered the confirmatory reference test. Both tests had to be positive in order to confirm HSV-2 sero-positivity. HSV-1 sero-status was also determined using these laboratory tests. Cytomegalovirus exposure was defined as ever having a positive CMV antibody, and this was extracted from the participant's medical chart. Detection of CMV antibody was done at the St. Joseph's Hospital Hamilton Regional Laboratory Medicine Program Virology Lab using the Abbott AxSYM Microparticle Enzyme Immunoassay (MEIA). Participants completed self-report case report forms that asked questions about their social, demographic, sexual health and reproductive history including age, age of sexual debut, number of sexual partners, ethnicity, place of origin, risk factor for HIV acquisition, completed education, income, etc.

#### 2.3.2.2. Measuring outcome

HRQoL was the outcome of interest for the quantitative phase and statistical analysis. Self-report questionnaires measuring HRQoL including the MOS-HIV and the SF-12v2 were administered and scored.<sup>128,129</sup>

### 2.3.2.3. Measuring symptoms of depression and anxiety

Depression and anxiety symptomatology can be measured using rating scales including questionnaires whereby patients assess their own symptoms. The Hospital Anxiety and Depression Scale (HADS) is a self-assessment mood scale that was designed for use in non-psychiatric hospital departments measuring the two most common aspects of internalizing disorders present in a general medical practice, namely, generalized anxiety and depression.<sup>130</sup> Instead of covering all states of distress assumed by the term ‘depression’ including demoralization from prolonged suffering, reaction to loss, a tendency to undervalue oneself, a pessimistic outlook, etc., Zigmond and Snaith concentrated on the loss of pleasure response, or anhedonia, which is considered one of the two obligatory states for major depressive disorder.<sup>131</sup> Seven items in the questionnaire reflect symptoms of anxiety whereas seven reflect symptoms of depression, five of which focus on the state of anhedonia, each with a four-point (0-3) response resulting in a range of scores from 0 to 21 for both anxiety and depression symptomatology. A score of 7 or less indicates a normal range or non-case; scores of 8 to 10 indicate doubtful, but possible cases; and scores of 11 or higher indicate definite presence of the mood disorder, or ‘caseness.’<sup>130-131</sup> Zigmond and Snaith explored test-retest reliability in two separate cohorts of 50 outpatients ranging in age from 16 to 65; results were similar between groups. The depression sub-scale had 1% false positives and 1% false negatives whereas the anxiety sub-scale had 5% false positives and 1% false negatives.<sup>130</sup> A recent review by Bjelland et al of 747 studies concluded that the “HADS was found to perform well in assessing the symptom severity and caseness of anxiety

disorders and depression in both somatic, psychiatric and primary care patients and in the general population.”<sup>131,132</sup>

For the purposes of this study, the HADS was administered to measure anxiety and depression symptomatology in the study group. Anxious and/or depressive ‘cases’ were conservatively defined as having a HADS score of 11 or higher, rather than including probable cases at borderline abnormality with scores between 8 and 10. These ‘cases’ were coded as a dichotomous variable.

### *2.3.3. Cross-sectional data collection*

It was the goal to have all case report forms and self-report questionnaires completed and blood work collected at the same visit to ensure a true cross-section in time. Logistically, this was not possible. Some women did not complete their routine clinical blood work at the visit when they enrolled in the study, or they were unable to stay to complete the questionnaires and handed the paperwork in at a later date. Many women were not given the MOS-HIV to complete at their initial study visit, so a large proportion of the study group had to be followed up with at a subsequent clinic appointment to ensure a complete data set.

### *2.3.4. Sample size justification*

The effect size composite used to interpret HRQoL scores was applied to determine the necessary sample size to detect a small (0.2), moderate (0.5) and large (0.8) difference between groups as per Cohen’s definition (see Appendix A for calculations).<sup>23</sup> The formula for sample size requirements for a two-group comparison in Norman and

Streiner was utilized.<sup>133</sup> The null hypothesis forming the basis for the sample size calculation was that there was not a significant difference between groups. A type I error or false-positive rate (or  $\alpha$ ) of 5% was chosen, meaning that 5% of the time the null hypothesis would be rejected concluding in error that there was a significant difference between groups. A type II error or false negative rate (or  $\beta$ ) of 20% was chosen, meaning that 20% of the time the null hypothesis would be accepted when in fact there was a significant difference between groups. In order to detect a small (0.2) difference between groups, a sample size of 784, or 392 people per group, would have been required. In order to detect a moderate (0.5) difference between groups, 63 people per group would have been required. To detect a large (0.8) difference between groups, 25 people per group and an overall sample of at least 50 women would have been needed. As there were 25 HSV-2 negative and 64 HSV-2 positive women included in this study, the study had sufficient power to detect a moderate to large difference between groups, but was underpowered to detect small differences between groups.

There was also interest in understanding the power of the study to detect differences between groups with an overall sample size of 89 women, or 25 women in one group (HSV-2 negative) and 64 women in the other group (HSV-2 positive). Assuming a type I error rate of 5% and utilizing a harmonic mean of 40 people per group to determine sample size,<sup>133</sup> 15% power was achieved to detect a 2-point or small difference between groups, 61% power was achieved to detect a 5-point or moderate difference between groups and 95% power was achieved to detect a 8-point or large difference between groups (see Appendix A for calculations).<sup>133</sup>

## ***2.4. Quantitative statistical analysis***

### *2.4.1. Description of the cohort*

Descriptive statistics of the study group were computed including means and standard deviations for continuous variables and proportions for categorical variables including Herpesvirus serostatus (HSV-2, HSV-1 and CMV), anxiety and depression symptomatology, age, nadir CD4 cell count, current CD4 and log viral load, years HIV-positive, current receipt of HAART and treatment for HSV, ethnicity, place of origin, history of drug use and HIV risk factor. The continuous PHS and MHS of both the MOS-HIV and SF-12v2 were computed and assessed visually for normality using histograms.

### *2.4.2. Differences between groups by HSV-2 sero-status*

Independent samples-tests were utilized to determine differences in physical and mental HRQoL between HSV-2 and HIV co-infected women and women infected with HIV alone as measured by the MOS-HIV and SF-12v2. Levene's test for equality of variance was first applied to determine if the samples had equal variances or homogeneity of variance, which is an assumption of the independent samples-test.<sup>133,134</sup>

Pearson's Chi square test was used to determine differences in the prevalence of anxiety and depression symptoms between HSV-2 and HIV co-infected women and women infected with HIV alone as measured by the HADS. The Pearson's Chi square test was also used to statistically explore the socio-demographic and clinical characteristics on which women may have differed by HSV-2 sero-status, potentially influencing HRQoL based on the literature including age, current CD4 cell count, years

living with HIV, history of drug use including alcohol, marijuana, cocaine and opiates and ethnicity, that is, proportion of women who were African-born.

#### 2.4.3. *Multivariable regression modeling*

Multiple linear regression was employed in order to explore and specify the statistical linear relationship between physical and mental HRQoL, the dependent variables of interest, with multiple independent variables.<sup>133</sup> The following assumptions of regression were assumed: (1) linearity: a straight line relationship exists between the independent and dependent variables in the model; (2) independence: the dependent predictor variables (or “y’s”) in the model are independent of each other and the errors associated with one observation are not correlated with the errors of any other observation; (3) normality: for any value of X, the possible values of the residuals, or the difference between the estimated value and the actual value, are normally distributed; (4) homoscedasticity: homogeneity of variance exists, that is, variance is the same at all points along the regression line; and (5) model specification: the model should be properly specified including all relevant variables and excluding irrelevant variables.<sup>133,135,136</sup> It was also important to consider individual observations or outliers as well as collinearity or highly correlated independent predictor variables, which may have exerted undue influence on the linear regression model coefficients.<sup>136</sup>

Four multivariable linear regression models were created in SPSSv18 utilizing the PHS and MHS of both the SF-12v2 and MOS-HIV as the dependent outcomes of interest. The adjusted R-square, or coefficient of determination, for each regression model was assessed to determine how well the model fit the data as well as how much of the

variance or variability was accounted for based on the variables included in the model.<sup>134</sup>

Unstandardized beta coefficients for each clinical variable of interest were reviewed for statistical significance and contribution to the model. Homoscedasticity was visually assessed via scatterplots of residuals.

Initially, the following variables were included in each regression model: HSV-2 sero-status, age, nadir CD4 (as a surrogate measure of immunosuppression), years living with HIV, receipt of treatment for HSV (current or ever received), current receipt of HAART, depression “caseness” and anxiety “caseness.” These variables were chosen because of their demonstrable influence on HRQoL in the literature. HSV-2 sero-status, receipt of HAART and treatment for HSV and depression and anxiety “caseness” were dichotomized, whereas age, nadir CD4 and years living with HIV were scaled as continuous variables.

Because there was not a significant difference in the prevalence of depression and anxiety symptoms between women co-infected with HIV and HSV-2 versus women infected with HIV alone, these dichotomous variables were removed from the final models. It was also decided to remove receipt of treatment for genital herpes from the models; previous treatment for genital herpes was not independent of HSV-2 seropositivity, rather, these variables were highly correlated and would have introduced collinearity. Because African-born women were significantly more likely to be HSV-2 positive compared to non-African-born women and the variable ‘place of origin’ was potentially acting as an effect modifier in the relationship between HSV-2/HIV co-infection and HRQoL, an interaction term was computed and assessed in the regression modeling in order to better understand this dynamic. The interaction term was not found

to be statistically significant, therefore, was removed from the linear regression models. The final linear regression models included the PHS and MHS of the MOS-HIV and SF-12v2 as dependent outcomes variables with the following independent variables: HSV-2 sero-status, current receipt of HAART, age per 10 years, current CD4 cell count (at time of enrollment), and African origin.

## **2.5. Results**

The HSV/HIV Co-Infection study was initially established to understand the seroprevalence of Herpesviruses in women accessing care at the SIS clinic, therefore, the original goal was to enroll at least 100 women into the study. In the end, serology was available for 103 women, however, complete data including HRQoL summary scores was available for only 89 women. Although it was the goal to have all questionnaires and blood work collected at the same visit to ensure a true cross-section in time, this was not possible. A large proportion of the study group had to be followed up with at a subsequent clinic appointment to ensure a complete data set. In light of this, three out of 103 women for who serology results were available declined further participation. Eight out of 103 women were lost to follow-up as they had moved away or had not returned to the SIS clinic during the data collection phase. Incomplete questionnaires at the initial study visit resulted in 58.4% (n=52) of the cohort having HRQoL measured on two separate occasions; the SF-12v2 was completed first followed by the MOS-HIV at a subsequent visit.

Table 1 presents demographic and clinical characteristics of the 89 HIV-positive women who were included in the analysis. The cohort had a mean age of 42.2 years



(SD=9.4) and had been living with HIV for an average of 8 years (SD=4.8). The women presented with a mean CD4 cell count of 519 cells (SD=259) and a viral load of 2.5 log copies per ml of blood (SD=1.1 log copies). The majority of women (n=64, 71.9%) were on HAART at study enrollment, and 57.3% of those women on treatment were virally suppressed. The HIV transmission risk factor cited most frequently was heterosexual intercourse (82%) followed by injection drug use (3.4%) and exposure to blood products (3.4%). Thirty-eight women (42.7%) were Caucasian whereas 41 women (46.1%) were Black followed by First Nation (3.4%) and South Asian (2.2%); 41.6% of women were Canadian-born and 41.6% were African-born. The majority of women had completed secondary school education (42.7%) and college or trade school education (43.8); 13.5% of the women had also completed university degrees. Despite the levels of education achieved, 43 women (48.3%) were relying on social assistance and/or government benefits as their primary source of income followed by salaries of employment (41.6%) or self-employment (5.6%). The majority of women were living on an annual income of less than \$15,000 CAD per year (40.4%).

Sero-prevalence for HSV-2 and HSV-1 was high in this cohort with 64 (71.9%) and 53 (59.6%) of the women having positive serology for HSV-2 and HSV-1, respectively; 70 out of 85 women (78.7%) were antibody positive for CMV. Twelve women (13.5%) were currently on or had ever received treatment for symptomatic genital herpes. Seventeen women disclosed a history of symptomatic genital herpes, 14 (82.4%) of which were HSV-2 positive.

Prevalence of anxiety symptoms was high in this cohort with fifty-one out of 88 women (57.3%) being classified as anxious 'cases' as per the HADS. The prevalence of

symptoms of depression was similar to what would be expected in a clinical sample of people living with HIV/AIDS with 11 out of 88 women (12.4%) being classified as depressive “cases” as per the HADS; one woman’s HADS score was not available.

The mean MOS-HIV PHS was 50.8 (SD=11.4) ranging from 17.9 to 66.6 whereas the mean MOS-HIV MHS was 49.0 (SD=11.1) ranging from 16.5 to 67.4. The mean PHS and MHS of the SF-12v2 were similar at 49.9 (SD=10.4) ranging from 19.3 to 68.2 and 45.3 (SD=10.1) ranging from 17.0 to 66.1, respectively.

Table 2 presents statistical analyses conducted in order to explore differences in HRQoL and other contextual factors by HSV-2 sero-status. HSV-2/HIV co-infected women had a significantly higher PHS (52.5 vs. 46.4;  $p=0.027$ ) and MHS (51.0 vs. 44.0;  $p=0.007$ ) as measured by the MOS-HIV, respectively. The SF-12v2, on the other hand, showed no significant difference between HSV-2/HIV co-infected women versus women infected with HIV alone for both the PHS (49.8 vs. 50.0;  $p=0.924$ ) and MHS (45.8 vs. 43.7;  $p=0.471$ ). HSV-2/HIV co-infected women did not significantly differ from women infected with HIV alone with regard to age (42.7 vs. 40.8 years;  $p=0.401$ ), current CD4 cell count (538 vs. 471 cells;  $p=0.282$ ) and years living with HIV (7.9 vs. 8.4 years;  $p=0.663$ ). HSV-2/HIV co-infected women were also not statistically significantly more likely to have symptoms of anxiety (Co-infected: 58.7% vs. mono-infected: 56.0%; OR=1.12, 95% CI 0.44-2.85), symptoms of depression (Co-infected: 9.5% vs. mono-infected: 20.0%; OR=0.42, 95% CI 0.12-1.53), or have a history of drug use (Co-infected: 15.6% vs. mono-infected: 12.0%; OR=1.36, 95% CI 0.34-5.41) compared to women infected with HIV alone. Women co-infected with HSV-2 and HIV were more

likely to be African-born (Co-infected: 48.4% vs. mono-infected: 24.0%,  $p=0.036$ ; OR=2.98, 95% CI 1.05-8.42).

Table 3 presents the findings from the multivariable linear regression models. The model exploring the relationship between HSV-2 sero-status and physical HRQoL as measured by the MOS-HIV had an adjusted R square value of 0.137, therefore, 14% of the variation in the physical HRQoL dependent variable was accounted for by the five independent variables included in the model. This model demonstrated that HSV-2/HIV co-infected women would have a 5-point higher score in their MOS-HIV PHS compared to HSV-2 negative, HIV-positive women ( $\beta=5.27$ ,  $p=0.046$ ); this unstandardized beta coefficient was significant at the  $p<0.05$  level. Being African-born was also associated with a statistically significant 6-point greater MOS-HIV PHS compared to non-African-born women ( $\beta=5.70$ ,  $p=0.018$ ). Last, the model showed that the MOS-HIV PHS was associated with a decrease of 2.5 points with every ten year increase in age ( $p=0.040$ ). The model exploring HSV-2 sero-status in relationship to the MOS-HIV MHS had an adjusted R square value of 8.3%, therefore, less variation in mental HRQoL as measured by the MOS-HIV was accounted for by the five independent variables included in the model compared to the model exploring the MOS-HIV PHS. HSV-2/HIV co-infected women had an almost 7-point higher score on their MOS-HIV MHS compared to HSV-2 negative, HIV-positive women ( $\beta=6.63$ ,  $p=0.013$ ). Also, women currently on HAART had a 5-point higher MOS-HIV MHS compared to women not on HAART ( $\beta=4.9$ ,  $p=0.061$ ), but this difference did not reach statistical significance.

The models developed to explore the relationship between HSV-2 sero-status and the PHS and MHS of the SF-12v2 accounted for significantly less variance (SF-12v2

PHS adjusted  $R^2=6.2\%$ ; SF-12v2 MHS adjusted  $R^2=1.1\%$ ) than the models developed with the MOS-HIV data. In the model exploring HSV-2 sero-status in relationship to physical HRQoL as measured by the SF-12v2, HSV-2/HIV co-infected had a 1.5-point lower SF-12v2 PHS compared to HSV-2 negative, HIV-positive women ( $\beta=-1.449$ ,  $p=0.561$ ), but this difference was not statistically significant. African-born women had a 5-point higher physical HRQoL score on the SF-12v2 compared to non-African-born women ( $\beta=5.22$ ,  $p=0.024$ ). No other independent variables included were statistically significant. No independent predictor variables including HSV-2 sero-status were statistically significant in the regression model exploring mental HRQoL measured by the SF-12v2 as the dependent outcome; minimal variation (1.1%) of the mental HRQoL score was accounted for by the five independent variables included in the model. Similar to the MOS-HIV regression models, the general trend was that current receipt of HAART would result in an one to two point increase in the PHS and MHS of the SF-12v2 (PHS:  $\beta=1.19$ ,  $p=0.627$ ; MHS:  $\beta=2.53$ ,  $p=0.306$ ). Every 10-year increase in age would result in an almost 2 point decline in PHS ( $\beta=-1.87$ ,  $p=0.109$ ) as measured by the SF-12v2.

The models with the PHS of the MOS-HIV and SF-12v2 as the outcome of interest had similar directionality and magnitude for the co-variables age per 10 years, current receipt of HAART, and African origin. In these two models, the HRQoL measures did not agree with regard to the magnitude, directionality or significance of HSV-2 sero-status (MOS-HIV:  $\beta=5.27$ ,  $p=0.046$ ; SF-12v2:  $\beta=-1.45$ ,  $p=0.561$ ). The models with the MHS of the MOS-HIV and SF-12v2 as the outcome of interest had similar directionality and magnitude only for the co-variables current receipt of HAART and HSV-2 sero-status, however, only the MOS-HIV MHS regression model found these

co-variates to be statistically significant. This conclusion must be considered in context; the SF-12v2 regression models developed for both the PHS and MHS did not account for much variance, that is, both models did not have goodness-of-fit as per the adjusted R-square values, and the p values of the individual co-variates included in the models (other than African origin in the SF-12v2 PHS model) were not statistically significant.

Scatterplots of the standardized residuals versus all predictor variables adjusted for in the models were created for all four linear regression models to visually assess homoscedasticity, or constancy of variance at all points along the regression line.<sup>136</sup> No patterns were observed in the scatterplots of the residuals plotted against the fitted values for each linear regression model, suggesting that homoscedasticity was present.

## **2.6. Discussion**

The purpose of this analysis was to explore the quantitative relationships between HIV and HSV-2 co-infection and physical and mental HRQoL of HIV-positive adult women from the Hamilton area. Univariable analysis via independent samples-tests found that HSV-2/HIV co-infected women had significantly higher physical and mental HRQoL as measured by the MOS-HIV compared to women infected with HIV alone; co-infected women had an almost 6-point higher PHS and a 7-point higher MHS compared to HSV-2 negative, HIV-positive women. These point differences showcase a moderate to large difference between groups as per Wu et al.'s direction for interpreting HRQoL scores.<sup>14</sup> Last, the linear regression model showed that the MOS-HIV PHS was associated with a decrease of 2.5 points with every ten year increase in age ( $p=0.040$ ), which is a biologically plausible association predicted by the model. The SF-12v2 data

presented a different story. HSV-2/HIV co-infected women had a 1.5-point lower PHS compared to HSV-2 negative, HIV-positive women; however, co-infected women had a 2-point higher MHS compared to women infected with HIV alone. Both the PHS and MHS SF-12v2 scores were not significantly different between groups in univariable analysis, and unstandardized beta coefficients computed in the linear regression models were also not statistically significant. The MOS-HIV data explored in univariable analysis failed to support the two hypotheses proposed at the beginning of this study including: (1) that HSV-2/HIV co-infected women would have a significantly *lower* mental HRQoL score compared to women living with HIV alone; and (2) that co-infected and mono-infected women would not differ by their PHS. The SF-12v2 data more closely aligned with the second study hypothesis that women would not differ significantly by PHS. It does not seem biologically plausible that HSV-2 infection would be the cause of an increase in either the PHS or MHS compared to mono-infection with HIV. There may be some other contextual factor confounding or modifying the relationship between HSV-2/HIV co-infection and HRQoL.

Linear regression modeling enabled an investigation into potential confounding or effect modifying variables in the relationship between HSV-2/HIV co-infection and physical and mental HRQoL. Univariable analysis highlighted the fact that women of African origin were more likely to be co-infected with HSV-2 and HIV; regression modeling brought to light the modifying effect of place of origin on the relationship between HSV-2 sero-status and PHS or MHS. Also, there may have been other contextual factors confounding or modifying the relationship between HSV-2 co-infection and HRQoL that were not captured in the regression modeling. For example, a

higher educational level or household income may have existed among co-infected women compared to mono-infected women, which may have influenced the positive relationship between HSV-2/HIV co-infection and HRQoL.

Overall, it was concluded that although women's HRQoL scores on the MOS-HIV or SF-12v2 differed depending on their HSV-2 sero-status, place of origin, receipt of HAART, etc., HSV-2/HIV co-infected women did not have significantly different HRQoL scores compared to women infected with HIV alone. This conclusion was drawn on the basis of only fair goodness-of-fit of the linear regression models determined by the adjusted R square values, the statistical significance of the unstandardized beta coefficients in all four models as well as the biological implausibility and divergence with the literature that HSV-2 sero-positivity would predict a better perceived physical and mental HRQoL.

Agreement between HRQoL measures is another issue that should be considered when drawing conclusions about the relationship between HSV-2 sero-status and physical and mental HRQoL in HIV-positive adult women. The MOS-HIV and SF-12v2 PHS linear regression models were aligned with comparable directionality and magnitude for a number of co-variables including age per 10 years, current receipt of HAART, and African origin; however the HRQoL measures did not agree to the same extent for HSV-2 sero-status with the MOS-HIV placing greater predictive power in HSV-2 positivity compared to the SF-12v2 (MOS-HIV:  $\beta=5.27$ ,  $p=0.046$ ; SF-12v2:  $\beta= -1.45$ ,  $p=0.561$ ). The two models exploring MHS had even poorer agreement with similar directionality and magnitude for the variable current receipt of HAART only. Similar to the PHS models, magnitude and predictive power of HSV-2 sero-status differed between the MHS

models (MOS-HIV:  $\beta=6.63$ ,  $p=0.013$ ; SF-12v2:  $\beta= 2.24$ ,  $p=0.372$ ). These discrepancies may be the result of the different HRQoL domains that are captured in the MOS-HIV, but not in the SF-12v2. The domains cognitive functioning, health distress and health transition are captured in the formulae when computing the MHS for the MOS-HIV,<sup>13,14,20</sup> but these domains are not represented in the SF-12v2. More broadly, there may be a problem with using the MOS-HIV to measure HRQoL in this group of patients.

Another hypothesis proposed was that women co-infected with HSV-2 and HIV would have a higher prevalence and severity of anxiety and depression symptoms as measured by the HADS compared to women living with HIV alone. Although women are especially at risk for psychological distress and depression,<sup>47,48</sup> and the prevalence of anxiety symptoms was high in this cohort, co-infected women did not have a higher prevalence of anxiety symptoms compared HSV-2 negative, HIV-positive women. The prevalence of depression symptoms was similar to what would be expected in a clinical sample of people living with HIV, but the prevalence of depression symptoms did not differ by HSV-2 sero-status. Because univariable analysis did not demonstrate anxiety or depression symptomatology to be a potential confounding factor in the relationship between HSV-2 sero-positivity and physical and mental HRQoL, these variables were not included in the linear regression models. Although the proportion of women with anxiety symptoms was similar between women with a history of symptomatic genital herpes (10 out of 17, or 58.8%) and those without a history of genital herpes symptoms (41 out of 71, or 57.7%), the high prevalence of anxiety symptomatology in this study group is relevant to the clinical management of HSV-2 infection, as mental and physical stress have been shown to be triggers and significant predictors of genital herpes recurrence in



women living with HIV and HSV-2.<sup>44,111</sup> Monitoring symptoms of anxiety may decrease the onset of genital herpes symptoms, thereby minimizing the potential for symptomatic HSV-2 to influence women's perceived physical and/or mental HRQoL. HIV-positive women with symptomatic HSV-2 infections may benefit from stress management interventions, which would enhance stress awareness, coping and relaxation skills.<sup>117</sup> Enhancing the stress management skills of these women would potentially defend against stress-induced immunosuppression and recurrence of HSV-2 symptoms, thereby improving overall HRQoL and well-being.<sup>117</sup>

The MOS-HIV and SF-12v2 are both normalized to the 1998 United States population with a mean of 50 and a standard deviation of 10.<sup>13,14,20</sup> Previous studies have demonstrated that people living with HIV/AIDS generally have lower physical and mental HRQoL compared to the general population, therefore, it was expected that this group of women would have significantly lower PHS and MHS scores than the mean value of 50 seen in the general population. The mean MOS-HIV PHS and MHS were 50.8 and 49.0, respectively, and the mean SF-12v2 PHS was 49.9. MOS-HIV PHS and MHS scores aligning closely with those seen in the general population may be attributed to the successful clinical management of HIV/AIDS and the transition of HIV infection to a chronic illness. Closely aligning HRQoL scores with the general population also highlights that the MOS-HIV and SF-36, the generic HRQoL measure from which the SF-12v2 was derived, were developed at a time when an HIV diagnosis denoted a death sentence and perceptions of HRQoL and well-being manifested in entirely different medical and social climates. The SF-12v2 MHS was the only summary score that was significantly different than that found in the general population. The SF-12v2 MHS was

45.3, a moderate effect size or 0.5 standard deviations lower than that found in the general population. This lower MHS may reflect the study group having a lower perceived mental health because of persisting stigma and marginalization related to their HIV status regardless of maintaining good physical health. This difference may also reflect variation in the psychometric properties between the MOS-HIV and SF-12v2.

There are limitations to this quantitative phase and statistical analysis that must be considered. First, the quantitative phase relied on cross-sectional data to draw conclusions about the relationship between HSV-2/HIV co-infection and HRQoL. In cross-sectional studies, the exposure(s) and outcome of interest are measured at the same time, therefore, it is impossible to determine true cause and effect, or causal, relationships between variables of interest.<sup>99</sup> The ideal study design would have been a prospective cohort study, assessing changes in HIV-positive women's HRQoL from the time of infection with HSV-2. Second, the appropriateness of the MOS-HIV to measure HRQoL in a group of HIV-positive women between 2005 and 2009 must be considered. Wu<sup>14</sup> has pointed out that the MOS-HIV has had relatively little use in research studies involving women, people with lower socioeconomic status and injection drug users; questionnaire administration may also need to be tailored to accommodate lower literacy and/or educational levels.<sup>3</sup> The population included in this cross-sectional analysis were all women. A large proportion of these women (48.3%) were relying on social assistance and/or governmental benefits as their primary source of income and the majority were living on an annual income of less than \$15,000 CAD despite levels of education achieved. The ability and trustworthiness of the MOS-HIV to measure HRQoL in a group of HIV-positive women remains to be seen. Another limitation of the MOS-HIV

as per Wu is that it does not delve into specific problems or concerns of HIV-related conditions and does not include some general aspects of HRQoL including sleep patterns, eating habits and sexual functioning,<sup>13,14</sup> the latter of which was especially relevant to this study looking at HSV-2 and HIV co-infection in women. Third, the convenience sampling strategy employed may have introduced selection bias as women who were engaged in research at the SIS clinic and agreed to participate in this study may have been demographically, clinically or socially different than women who were not approached to participate or who declined participation.<sup>99</sup> To ensure a diverse and expansive study group, as many women accessing care at the SIS clinic were approached as possible from July 2005 until July 2008. Fourth, research personnel may have been aware of the HSV-2 sero-status of potential participants prior to obtaining informed consent. Previous genital herpes outbreaks, HSV-2 infection symptomatology and/or previous exposure to or current use of episodic or suppressive HSV therapy would have been captured in potential participants' medical records, which were screened prior to women attending routine clinic appointments. Although as many HIV-positive women who access care at the SIS clinic were approached during the enrollment period as possible in order to ensure a representative sample of the broader female HIV population at the clinic, it is unknown how prior knowledge of genital herpes outbreaks, therefore their HSV-2 sero-status, may have influenced recruitment and enrollment practices and priorities, as well as the study results. Last, as discussed in the sample size justification and power calculation, with 25 HSV-2 negative and 64 HSV-2 positive women included in this study, the statistical analysis was able to confidently detect a large difference between groups, but was underpowered to detect small and moderate differences between

groups, which would have influenced the interpretation of the univariable and subsequent multivariable analyses.

The introduction of combination antiretroviral therapy has facilitated remarkable decreases in HIV-related morbidity and mortality, and HIV is increasingly viewed as a chronic illness. HRQoL assessments from the perspective of patients will become increasingly important as life-prolonging antiretroviral treatments are refined, especially considering that one goal of treatment is to find the most tolerable and effective regimen while maximizing quality of life and well-being.<sup>3</sup> As people living with HIV/AIDS continue to face complex health-related challenges such as co-morbid health conditions and/or co-infections, it is essential to incorporate HRQoL into treatment and care planning.

### ***2.7. Concluding statements, researcher reflexivity and linking quantitative with qualitative***

Overall, the goal of this quantitative phase was to understand the relationship between HSV-2 and HIV co-infection and HRQoL. Quantitative, positivist research methods with a heavy reliance on questionnaires and laboratory markers were utilized to explore these relationships. Although the clinical investigative team decided to recruit over 100 women to ensure adequate sample size and power for statistical analyses, this study was not originally designed to include the narratives of women living with HIV and HSV-2.

I started working as a student in the SIS clinic and took over coordination of the study in 2006 in order to strengthen my knowledge and skills related to research project

management, data collection and analysis techniques as well as engaging HIV-positive women in the clinical research process. Throughout my involvement in the project, I developed relationships with the women who were participating. I concluded that although the positivist, quantitative data collection tools being used were important and pivotal to understanding cause and effect, they were unable to bear witness to the everyday lived experiences of these women. The questionnaires employed could not capture nor explore the broader social, political and cultural contexts in which these women were situated from the perspective of living with HIV and genital herpes. Typically, research on sexually transmitted viral infections (STVIs) including human papillomavirus (HPV) and herpes simplex virus (HSV) have focused on epidemiology, pathogenesis and treatment, with less attention paid to how people live with and adapt to these chronic illnesses.<sup>137</sup> Qualitative research has demonstrated, however, that having a STVI can have a significant impact on individuals with regard to perceptions of stigma, mood and expression of sexuality, as well as their relationships by altering sexual behaviour or being a source of conflict within relationships.<sup>138</sup> Society has relegated people with STVIs to a lower social standing and has reframed ubiquitous viral infections into taboo subjects causing those affected to feel shame and guilt. In speaking with the women informally during clinic appointments, I knew that the questionnaires being used would not capture other issues that they linked to living with HIV and genital herpes, that is, issues of disclosure, criminalization of STIs, body image, sexuality and sexual health.

When I began my graduate program in July 2008, I understood the power of combining positivist, objective quantitative research methods with interpretive, subjective qualitative research methods to comprehensively understand a phenomenon, and realized

that I was in a position to explore a clinical issue while bearing witness to these women's narratives and enabling their voices and experiences to be heard through alternative research methodologies.

The next section of this thesis will explore the qualitative phase of this mixed methods study, which was informed by interpretive phenomenology philosophy and methodology. The goal of this phase was to give a voice to individuals who are often marginalized and stigmatized because of illness, and describe women's experiences in their own words thereby illuminating their realities and vulnerabilities.

## Chapter 3

### HIV-positive women's experiences of living with symptomatic HSV-2 infection and their perceived HRQoL: a qualitative interpretation

#### 3.1. *Research tradition*

The qualitative phase of the study was conducted in order to build upon and further explain the associations investigated in the quantitative phase. Interpretive phenomenology informed by the philosophical perspective of Heidegger and the social constructivist paradigm was employed to explore the lived experience of HIV-positive women living with symptomatic HSV-2 infection, or genital herpes.<sup>139,140</sup> Interpretive phenomenology was an appropriate qualitative research tradition for this study because of the goal to explore and understand meaning that HIV-positive women ascribed to the phenomenon of interest, contextualizing this meaning in their culture, social location and temporal context.<sup>139-141</sup> Conclusions drawn aligned with the general tenets of naturalistic inquiry whereby themes and concepts were grounded in the data instead of deducing testable hypotheses from existing theories.<sup>142,143</sup> Also, themes and concepts that emerged focused on the perspectives of study participants who experienced the phenomenon without imposing a priori conceptualizations or prepositions.<sup>139,143,144</sup>

Interpretive phenomenology acknowledges and integrates the beliefs, assumptions, preconceptions and biases of the researcher into the development, data collection, analysis and interpretation phases of the study, enabling an iterative and conscious exploration of “being-in-the-world,” taking the researcher from a “dazed perspective” to a “gazed perspective” of reflecting and understanding the “whatness” of ordinary life.<sup>145</sup> This iterative and conscious exploration of meaning is collaborative in nature; the researcher enters into a co-created, hermeneutic circle of understanding that

blends the meanings shared by participants with the interpretations articulated by the researcher.<sup>141,146</sup> Hermeneutical phenomenology aligns with the social constructivist philosophy proposed by Charmaz whereby hierarchies of power, social interactions and complexities of local worlds, views and actions are highlighted while minimizing power relationships between the researcher and study participants.<sup>142,144,147</sup> Charmaz advocates for maintained reflexivity of the researcher viewing the process of category and theme development as dialectical and active.<sup>142,147</sup> The philosophical underpinnings of interpretive phenomenology and social constructivism were combined in this study in order to highlight and contextualize the voices of HIV-positive women. Descriptive phenomenology from the perspective of Husserl was not chosen as a qualitative research tradition because it was not the goal of this study to describe the essential structure of the phenomenon, nor was it possible to bracket the presuppositions, biases or values of the researcher resulting in an “investigator-free” description of the phenomenon.<sup>139,141</sup>

### ***3.2. Qualitative research question***

What meaning do adult women who access care at the SIS clinic in Hamilton, Ontario currently ascribe to living with HIV and symptomatic HSV-2 infections in relationship to their physical and mental HRQoL?

### ***3.3. Sampling strategy***

The sample of the qualitative phase included women 18 years of age or older living with HIV and symptomatic HSV-2 infections who were already enrolled in the quantitative, cross-sectional phase of this study. Women who screened sero-positive for



HSV-2 by a prior blood test conducted in the quantitative phase and who had a history of genital herpes symptoms or had received treatment for genital herpes in the past were invited to participate. Women were invited to participate as they attended routine clinic appointments at the SIS clinic from December 2009 until March 2010 after HHS/FHS Research Ethics Board approval had been received for this phase of the study.

The aim of the qualitative sampling strategy was to involve information-rich individuals to enable a comprehensive understanding of HIV/HSV-2 co-infection, not to ensure population representativeness.<sup>143,144,148</sup> Purposeful sampling was utilized whereby HIV-positive women 18 years of age and older were invited to participate because they had particular knowledge of the phenomenon of interest that could purposefully inform the research question.<sup>139,149</sup> Criterion and convenience purposeful sampling typologies were combined in this study. Criterion sampling involved applying the eligibility criteria when reviewing SIS clinic appointment lists and medical records of women enrolled in the cross-sectional phase of the study. Convenient sampling was employed as women were asked to participate as they attended routine, scheduled clinic appointments. Women had to be able to speak and communicate in English in order to participate in an interview. To encourage multiple perspectives and engage women from different communities in the research process, no one was excluded on the basis of ethnocultural background, sexual identity, socioeconomic status or other demographic or clinical characteristics.<sup>148</sup> Women across the age range of 18 to 60 were sought. It was felt that the heterogeneity in participant demographics would potentially present challenges during the data analysis and interpretation phases as variation in perceptions of physical and mental HRQoL may exist among women who differ by ethnocultural group, age,

sexual orientation, etc. Because these women came forth expressing interest to participate and share their story, however, they were not turned away. A homogeneous sample is appropriate for phenomenology as it focuses the attention of the study to the phenomenon of interest.<sup>150</sup> Enforcing strict criteria that excludes or limits the multiple perspectives and realities of potential participants, however, contradicts the philosophical underpinnings of interpretive phenomenology where participant-centered recruitment and sampling approaches are employed and the subjective, self-determined and self-described realities of individuals and groups are actualized.<sup>145</sup>

Sample sizes in phenomenological studies are typically small and can range from a small study of one participant to studies involving between 20 and 50 participants.<sup>139,151</sup> Morse has recommended that phenomenological studies interested in understanding the essence of experiences include about 6 participants,<sup>152</sup> whereas Van Kaam has recommended including 10 to 50 descriptions of a phenomenon of interest in order to understand it in a comprehensive and in-depth manner.<sup>153,154</sup> Although predetermination of sample size is impossible, it was the goal to involve about 6 to 10 women in this phenomenological study enabling an in-depth exploration of the relationship between living with HIV and symptomatic HSV-2 infections and HRQoL.

### ***3.4. Qualitative data collection***

In interpretive phenomenology, the interview serves as a means to explore and gather experiential narrative material that will serve as a resource to develop a richer and deeper understanding of the phenomenon, as well as a vehicle to develop a conversational relationship with an interviewee about the meaning of their experience.<sup>155,156</sup> After

informed consent was obtained, study participants underwent an in-depth, semi-structured, face-to-face interview approximately 1 to 1.5 hours in duration with the author.

A semi-structured interview schedule was developed to ensure that the same concepts were explored with each participant, while remaining flexible to allow for the emergence of other issues that may not have been anticipated and to not impose a priori categorizations that may have limited inquiry.<sup>148,157,158</sup> The interview schedule was based on the quantitative analysis that was conducted in the first phase and was pilot tested with the first interview participant. Following the pilot interview, the wording and flow of the interview schedule questions was adjusted. Probes were introduced throughout the interview to explore in greater depth participant's perceptions of the relationship between HIV and symptomatic HSV-2 infections and physical and mental HRQoL, however, as stated by van Manen, "the art of the researcher in the hermeneutic interview is to keep the question (of the meaning of the phenomenon) open, to keep himself or herself and the interviewee oriented to the substance of the thing being questioned."<sup>155</sup>

The interview schedule incorporated open-ended questions asking about factors or dimensions of HRQoL that were and were not statistically significant in the quantitative phase but were important elements identified in the literature.<sup>125</sup> Prior to starting the interview, participants were presented with the information and consent form, and the purpose of the interview, the nature of questions to be asked and the duration were discussed. The following questions were asked during the interview:

*General health*

1. What comes to mind when you think about your health?
2. What comes to mind when you think about your physical health specifically?

What improves or worsens your physical health?

3. What comes to mind when you think about your mental health specifically?  
What improves or worsens your mental health or emotional well-being?

*Living with HSV-2 as an HIV-positive woman*

4. As an HIV-positive woman with genital herpes, I wonder what that has been like for you. Please tell me about your experience living with HSV-2 infection or genital herpes as a woman also living with HIV.
5. Does living with genital herpes impact your physical health (e.g. physical functioning, bodily pain)?
6. Does living with genital herpes impact your mental health (e.g. emotional well-being, self-esteem, self-confidence, fear of transmission, uncertainty of long-term general health, body image, stress, anxiety, etc.)?
7. Does living with genital herpes affect your day-to-day functioning (e.g. ability to perform at work or in school)?
8. Does living with genital herpes impact your relationships (e.g. ability to have social relationships, intimacy, attitudes towards sex, disclosure to partners, sexual functioning, sexual satisfaction, freedom and spontaneity, etc.)?
9. How do you experience your sexual self as a woman living with Herpes and HIV?

*Receiving treatment for herpes*

10. Are you currently or have you ever received treatment for genital herpes (i.e. acyclovir, Valacyclovir/Valtrex, etc.)? Please tell me about your experience receiving treatment.
11. Does, and if so, in what way, does treatment for genital herpes affect physical health?
12. Does, and if so, in what way does treatment for genital herpes affect mental health?
13. Does, and if so, in what way, does your HIV status play into receiving treatment for genital herpes?

*Perceptions of quality of life*

14. Upon reflecting and thinking about the stories and feelings you have shared throughout our conversation today, I'm now wondering what you think about the term "quality of life?" What does the phrase "quality of life" mean to you?  
What negatively affects your quality of life?  
What positively affects your quality of life?

The author strove to establish an interview setting that was conducive to "collaborative hermeneutic conversations," enabling participants to reflect on their experiences.<sup>155</sup> The philosophy that underlined all data collection methods was that the subjective experience of participants was valued. In interpretive phenomenology each individual is considered an active agent interpreting their own experience and creating themselves by their inner existential choices;<sup>145</sup> meaning comes from the source and is not presumed, assumed or assigned.<sup>156</sup>

Women were provided a \$50 honorarium as a token of appreciation and to cover any costs incurred while participating, for example, parking. All in-depth interviews were digitally recorded and transcribed verbatim. Transcripts were cross-referenced with the digital recordings following transcription to ensure accuracy. NVivo8 computer software was used to electronically manage and code the interview transcript data.

### *3.5. Qualitative analysis*

Hermeneutic phenomenological reflection and thematic analysis proposed by van Manen was employed whereby themes, defined as textual statements that are “the means to get at the notion, ... give shape to the shapeless, and ... describe the content of the notion,”<sup>155</sup> were isolated and highlighted to elucidate the meaning or essence of the relationship between HIV and symptomatic HSV-2 co-infections and HRQoL. This analysis framework aligns with the qualitative editing organizing style where the researcher acts as interpreter and editor, segmenting the data by identifying information most pertinent to the research question and then categorizing and splicing the text.<sup>159</sup> The process of uncovering thematic statements from the interview transcripts followed van Manen’s metaphor that “themes are not objects or generalizations...they are more like knots in the webs of our experiences, around which certain lived experiences are spun and thus lived through meaningful wholes.”<sup>155</sup> Three approaches to uncovering and coding thematic statements in the text were utilized including: (1) the holistic or sententious approach: a whole body of text (e.g. an entire interview, all interview transcripts) is reviewed; a rich yet brief statement is created in an attempt to capture the fundamental meaning or main significance of the text as a whole; (2) the selective or

highlighting approach: a particular body of text is read or listened to several times; statements or phrases that are interpreted as particularly essential or revealing about the phenomenon are selected; (3) the detailed or line-by-line approach: every single sentence or a small sentence cluster in a body of text is scrutinized to see what the sentence(s) reveals about the phenomenon of interest. The three approaches to coding and uncovering thematic statements were accompanied with note-taking to ensure that the composition of linguistic transformations was not a mechanical process, but rather was creative, circular and hermeneutic.<sup>155</sup> Recognizing that themes are multi-dimensional and multi-layered, the analysis framework attempted to differentiate between incidental and essential themes. As per Van Manen's thematic analysis recommendation, themes were scrutinized by asking if the phenomenon would be the same if a theme deduced from the text was imaginatively changed or deleted.<sup>155</sup> Not all meanings encountered in textual data are unique to the particular phenomenon or lived experience of interest; only essential themes that were intimately linked to the relationship between HIV/HSV-2 co-infection and HRQoL were included in the analysis and phenomenological narrative.

To increase rigor of the study, Van Manen describes member checking as an opportunity for the researcher and interviewee to collaborate and engage in a follow-up hermeneutic conversation once transcript themes have been identified by the researcher.<sup>155</sup> Together, the researcher and interviewee interpret the significance of the preliminary themes in light of the original phenomenological question, weighing the appropriateness of each theme identified. Although member checking would have added methodological rigor to this qualitative study, due to time and resource constraints, it was not possible to meet with interview participants more than once. Van Manen places

equal importance on collaborative conversations with research team members regarding emergent themes; these meetings were a significant component of the qualitative analysis and interpretation.<sup>155</sup> Peer debriefing was the author's opportunity to converse, question and "place in the open" the narratives shared by the women and the researcher's interpretation of these narratives.<sup>155</sup> The author had in-person meetings with Dr. Saara Greene on three separate occasions throughout during the data collection and analysis. The purpose of these meetings were to review and finalize the pilot interview schedule following the initial in-depth interview, discuss preliminary emerging themes after five of the seven interviews had been completed, and to critically review the author's interpretation of the women's narratives after coding and analysis of all qualitative data. There was also an opportunity at each meeting to discuss data collection methodology, interview facilitation skills of the author, researcher and participant dynamics during an interview including the role of emotions experienced by either, and how these issues may have affected data collection, analysis and interpretation.

A secondary literature review was conducted after completion of the data collection, analysis and peer debriefing phases in order to link the interpretation with existent literature. Articles found that were relevant to emergent themes and concepts were woven into the interpretation and discussion.



### ***3.6. Findings***

Seven women who participated in the cross-sectional, quantitative phase of this study agreed to participate in an in-depth interview to discuss their experiences living with symptomatic HSV-2 infection, or genital herpes. A total of ten women were approached to participate in an in-depth interview, however, three women declined citing lack of comfort in discussing their experience living with genital herpes. The women had an average age of 46 years ranging from 38 to 57 years. The average number of years that the interview participants had been living with HIV was 11 years, ranging from 2 years (one woman) to 18 years (four women had had HIV for 14 to 18 years). All of the women had acquired HIV through heterosexual intercourse, and one woman additionally had a history of injection drug use. Five of the women described their ethnicity as Canadian-born Caucasian, one woman identified as Canadian-born Aboriginal and one woman identified as Black with Caribbean descent. Five of the women had been living with symptomatic genital herpes for the same amount of time as living with HIV, one woman began having outbreaks a few years after her HIV diagnosis and one woman had had genital herpes prior to receiving her HIV diagnosis. Four of the participants were using suppressive therapy for their genital herpes at the time of the interview, whereas two of the women had not had outbreaks in a few years, therefore only used HSV treatment when needed or on an episodic basis. One participant had never taken episodic or suppressive therapy for her genital herpes, even though she had had symptoms. All interview participants were given a pseudonym to protect their identity and privacy, which was used throughout this thesis to highlight individual woman's narratives.

All participants were asked a number of open-ended questions regarding perceptions of their physical and mental HRQoL in the context of living with HSV-2/HIV co-infection, specifically, women were asked to consider and express the meaning that they ascribed to their HRQoL in relationship to living as a woman with HIV and genital herpes. A number of themes were identified that women uniquely associated with HSV-2 alone and HIV alone, as well as themes that were associated with being co-infected with HIV and HSV-2. All of the themes that women discussed in relationship to HSV-2 and HIV were either aligned with good or poor physical and/or mental HRQoL.

It was clear from the participant narratives that although women were co-infected with two sexually transmitted and chronic viral infections, they experienced these conditions very differently. It was important to first explore the impact of HIV on perceived HRQoL before understanding how living with HSV-2 affected HIV-positive women's physical and mental HRQoL. How women described living with HIV was important to understanding their global HRQoL; their narratives shed light on their social and historical contexts, as well as the journeys that had brought them to where they were at today. How women described living with HSV-2 or genital herpes, on the other hand, was important to understanding their day-to-day functioning and episodic HRQoL, as HSV-2 was presented as more of a periodic and acute issue that was sometimes a more dominant concern in their life compared to their HIV infection. Some themes that women uniquely associated with HSV-2 were gendered because they had a stronger influence and impact on their experiences as women. For example, because HSV-2 infection was discussed in relationship to day-to-day functioning and episodic HRQoL, its affect on physical and mental health closely aligned with the gendered social roles that

women assumed including the caregiver and sexual partner. Realizing this distinction between HIV and HSV-2 enabled an in-depth analysis of how genital herpes compounds and complicates the lives of HIV-positive women. The participants discussed a number of themes that facilitated achieving and maintaining good physical and mental HRQoL including: asserting their identity as HIV-positive women living with genital herpes; maintaining stability in their life, which included the stability and routine of treatment for HIV and HSV; having access to social and spiritual support; and setting and maintaining boundaries in relationships including having clarity regarding their social roles. There were some aspects of living with both chronic, viral infections that prevented women from maintaining good physical and mental HRQoL including feelings of uncertainty about their futures, episodes of sickness and poor health, fear and anxiety related to their HIV status, insecurity regarding their identity and body image, and experiences of HIV-related stigma.

### *3.6.1. The journey to good physical and mental HRQoL: acceptance of HIV status*

The ability to achieve good physical and mental HRQoL in the first place rested on how women perceived and where they were at in their journey to acceptance of their HIV status. For example, when and how they had become infected as well as their historical experiences of HIV-related stigma had the power to prevent them from or to support them in moving forward in their lives as HIV-positive women. In the participant narratives, achieving good physical and mental HRQoL was associated with the work that they had done to shift self-perceptions and enable themselves to be “in a good place.”

The women who identified having a good quality of life projected positive and healthy perceptions of their identity and body image, and these positive perceptions of self were expressed in an assertive and confident manner throughout the interview dialogue.

“The way HIV is affecting my life more, I think is about how I decided to deal with it, and I, you know, I was kind of one of the people who felt like, ‘OK, I have this, I must have it for a reason,’ like (laughs), like I have just sort of justified it somehow. And so I really became very passionate about working in the community, at first as a volunteer and now actually making a career out of working in the community...learning a lot of new things and a lot of new skills, so in many ways this has actually been really good for me because I am very passionate about it, I really believe in following your place and your passion...in many ways it's actually helped me sort of to reach some of the goals in my life” (Shirley, age 47).

Shirley’s narrative links a positive self-perception with a desire and ability to work in and give back to her community. Acceptance of her HIV-positive status has transformed into a passion and motivation to develop professionally, and ‘living with HIV’ is the expert knowledge that she brings to different career opportunities.

Some women highlighted the temporal nature of self-perception and how their identities had changed over time, depending on where they were at in their journey to acceptance of living with HIV.

“Sometimes, um, my thinking goes like, good, where all this really does not really matter because it’s all brought me to who I am today and I am a good person... I have done some crappy things in the past right and but today I am a good person” (Tabitha, age 38).

During the interview, Tabitha reflected about her life and how her identity had changed over time to one where she now considers herself a ‘good’ person regardless of the fact that she is living with HIV and genital herpes.

The assertive and confident perceptions of self held by some of the women were juxtaposed with an awareness of the existence of HIV-related societal and institutional stigma. Women may have possessed and presented a healthy self-perception and body image during the interview, but they had awareness of and were cautious to hold their identities close when they felt unsafe or where they had witnessed HIV-related stigma. Joni's story about considering herself a 'beautiful person,' but not feeling comfortable disclosing her status at work as a woman co-infected with HIV and HSV-2 demonstrates this juxtaposition:

“The other people that I work with they say, you know, oh, he is dirty... meaning that he has got AIDS or HIV positive...I think to myself um, if only you knew, you know? I am dirty too...But I don't think of myself as dirty. I think of myself, like I said, as a great person. I think I am a great catch. I have just got these two, okay, one little problem and a big problem, if that is the way you want to look at it...A lot of people got it for whatever way they got it, it does not make you a bad person...and, well, I guess my blood is dirty...but you know what? I got it under control, you know, and I am still a beautiful person, you know, so who cares?” (Joni, age 51).

Women's experiences of stigma throughout their journeys to acceptance sometimes interfered with their ability to maintain good or positive physical and mental HRQoL. Women who had come to terms with living with HIV and HSV-2 presented a positive perception of self and comfort with their identity. As articulated by Tabitha, HIV and genital herpes did not define who they were, but, instead, it was a part of them:

“It's not who I am, it is a part of me...Because before when I was younger I actually believed that I was the disease...That is how I actually felt, um, that is what people told me” (Tabitha, age 38).

Tabitha's narrative reflects societal shifts in beliefs and perceptions of HIV, as well as how the progression and evolution of the HIV epidemic has enabled women to claim and assert their identities as HIV-positive women.

### 3.6.2. *Genital herpes and HRQoL of HIV-positive women*

Living with genital herpes, or symptomatic HSV-2 infection, affected HIV-positive women's perceived physical and mental HRQoL by creating disruptions and fluctuations in the dynamic between 'being' and 'not being' in a 'good place.' Although women spoke of ways in which genital herpes affected perceptions of their mental and physical health and subsequent quality of life, in the grand scheme of things, HSV-2 infection and genital herpes outbreaks was not their primary concern. Genital herpes was viewed differently than HIV; it was an 'issue' that they were managing in their life in addition to their HIV. Genital herpes was not something that predominantly dictated their global HRQoL, instead, it was a concern that presented itself and that they had to deal with on an episodic basis, for example, when they were experiencing a herpes outbreak.

To what extent women expressed concern regarding their HSV-2 infection and genital herpes outbreaks was related to how much they had accepted their HSV-2 and HIV diagnoses and their level of knowledge regarding the medical implications of being HSV-2/HIV co-infected. For Shirley, although she had had herpes for many years, the act of reflecting and discussing her experiences during the interview stimulated new emotions of confusion and consciousness:

“I didn't really realize, like, that I was really infectious. Like, I don't think I had all the right information...even though I have known I have had it for a long time, for me it's almost like a new diagnosis because I never really realized, like, Oh, if I don't have herpes on my genitals I could still transmit herpes...I never really disclosed it to sex partners before because, like I said, I didn't...really know” (Shirley, age 47).

Shirley had recently increased her knowledge regarding HIV/HSV-2 co-infection. Her narrative highlighted not only the confusion and misinformation that women may have regarding the medical implications of being HIV and HSV-2 co-infected, but the

subsequent realization and anxiety that women may experience when it is learnt that HSV-2 can be transmitted regardless of its latency and where the outbreaks occur on the body. Shirley's realization prompted reflection and consideration regarding disclosure of HSV-2 infection to partners along with her HIV status:

“I am actually more conscious of having to disclose the herpes now than the HIV! Because now, you know, since I realized that I could actually infect somebody...it's kind of a bit stressing...there's been partners I have not disclosed that to and so I am concerned about that...HIV, I am not really worried about, you know, passing HIV to anybody because it's under control and I use, practice safe sex...but now I have this, like, this other thing to think about, herpes...I think that it's, you know, it's more infectious, even than HIV” (Shirley, age 47).

Shirley ultimately decided that disclosure of one's HSV-2 infection was just as important as the legal obligation to disclose one's HIV status. The acute stress and confusion that Shirley expressed during the interview eventually stabilized, causing only a slight disruption in the trajectory of her overall mental HRQoL.

To what extent women expressed concern regarding their HSV-2 infection or genital herpes outbreaks was also related to the level of agency and responsibility taken for their co-infections. Women who experienced disequilibrium in their physical and/or mental HRQoL status, including due to herpes outbreaks, did not describe good overall physical and mental HRQoL with the same level of assertiveness as those women who described having agency and ownership for their HRQoL status. An association was drawn between living with HIV and herpes and perceived HRQoL to decision-making, as well as if one took ownership of and responsibility for the choices and decisions made in life, including putting oneself at risk for HIV and HSV-2. Beverly's narrative threaded together her conscious choice to base all life decisions on her health with her regret for

putting herself at risk for HIV and herpes, which, ultimately, in her opinion, changed her life course:

“It’s the choices we choose and I made the biggest, shittiest choice of my life. I wish I could take that back. And I, and I spend a lot of my time just saying, yeah, what if, what if, but I try not to do that anymore cause it makes me cry” (Beverly, age 42).

Although throughout their interviews both Beverly and Ursula referenced having a good job, a nice home and a loving family, they expressed regret for becoming infected with HIV and HSV-2 and blame towards the people who had infected them. These emotions have perpetuated the episodes of poor health and poor perceived quality of life experienced by Beverly and Ursula. On the contrary, having ‘dealt her own hand,’ Ellen ‘chose to swim’ as an HIV-positive woman living with herpes:

“When I first found out I, I couldn’t even look in the mirror, just the thought of it just upset me greatly. Um, but after a while you just start to realize that this is who I am, this, these are the cards I have been dealt. I think the hardest part was the fact that I dealt my own hand, this is something that I, I could have controlled...but you can walk around and I can kick myself for the rest of my life or I can accept it, deal with it, get on with it and try to make the best of it... You can mope around in that uh, self pity for only so long and then you make a choice, you sink or you swim. So I chose to swim” (Ellen, age 45).

Similarly, Joni has chosen to deal with her ‘irritations:’

“I didn’t really know at first, I thought I was going to die, but then they explained to me that you could take meds and then you are like a normal person again. So even still that it is a hindrance in a way, I think of the positive. I am going to lead a normal life...my health is fine. I just got this irritation, that is all it is, is an irritation. So what, live with it...I am not going to let something little like herpes bring me down. I mean I don’t like the fact that I have it, I can’t change that so I am living with it and living my life to the best that I can” (Joni, age 51).



### 3.6.3. *Stability: a means to maintenance of good physical and mental HRQoL*

Women described maintaining stability in their lives as an important element to maintaining good physical and mental HRQoL; all women associated stability with HIV/HSV-2 co-infection, not HIV nor HSV-2 individually. One of the ways that women were able to ensure stability was through the control of HSV-2 outbreaks via suppressive therapy. In Shirley's case, HSV-2 therapy helped her to stay organized, not only to ensure that she didn't have herpes outbreaks, but also to ensure that she maintained compliance with her HIV medications.

“I can sort of feel it coming on before, like I have scars from where it breaks... And then if I don't, you know, start to up my dose of acyclovir it will actually turn into a sore. Usually it doesn't really get to that point. I usually just, you know, just keep eating acyclovir... I usually put my HIV meds in my, the herpes stuff and my arthritis stuff, all in, in a planner... If anything it makes me more adherent to the herpes treatment because I know I have to take my HIV meds, so I just do it all at the same time... Actually it even works in reverse, because I know that if I don't take the acyclovir then I am gonna feel like crap, so at the same time I remember to take my HIV meds. So they kind of compliment each other that way” (Shirley, age 47).

Beverly expressed dislike towards the need to constantly take her medication for HSV-2, but admitted the control and freedom that suppressive HSV-2 treatment permitted:

“Although I don't like to have to constantly take medication, I really hate it... but it does give me the freedom of, um, if I want to be intimate I can be. Um, and knowing that I have a little bit of control over it, and, that's big, yeah” (Beverly, age 42).

Although Beverly has not yet required any treatment for her HIV and she does not experience any adverse effects from HSV-2 therapy, taking medication for HSV-2 every day was an immense commitment for her. This suppressive treatment, however, has contained the worry and concern caused by the pain and irritation of genital herpes lesions enabling Beverly to get on with her relationships and her life.

Another way that women maintained stability was by controlling who in their life was aware of their HIV and HSV-2 status. Having control over who knew about their medical conditions reduced stress and anxiety in their lives. In Ellen's case:

“Anyone that I want to know, I have told in my life...so that weighs on my mind at times...If you come into my life, you are going to be, you know, in one of a few circles, the innermost circle they know, they understand because if something goes wrong, this is my support system...Then there is people who are in my life who are my, you know, friends or acquaintances who don't need to know, my mother doesn't know 'coz she doesn't need to know, she doesn't need that stress” (Ellen, age 45).

#### *3.6.4. Importance of social support*

All of the women identified formal and informal social support as an important and central element to achieving and maintaining good physical and mental HRQoL, even though each defined and used social support in different ways. Like some of the other women, Ellen had identified people in her life who she could trust and count on, and it was those people to whom she had disclosed her HIV status. Women shared the details of their medical conditions with people who they knew would not hold it against them, and who would be there in times of stress and difficulty. These people were not always family members, in fact, a few women chose not to tell family because of not wanting to cause stress and anxiety for family members, and because of fear of rejection and judgment by their families. With whom women had shared their status seemed to depend on how open or public they were about their HIV status, for example, how involved they were in the HIV community as service users, volunteers and/or advocates.

Supportive and fulfilling relationships with family and friends were important to maintaining stability and good HRQoL. For Ellen, it was important to have a group of

people in her life that supported her regardless of being HIV-positive and having herpes, whether they were aware of her status or not.

“Feeling a sense of fulfillment with my life. I think that, uh, relates to quality of life. In all different areas, um, in relationships and friendships, in relationships with my family, my kids, um, I have a job that I enjoy. Um, I have a very supportive group of people around me. So, things are good” (Ellen, age 45).

Access to and utilization of social support was a positive influence on women’s mental HRQoL. Women who expressed the importance of supportive and fulfilling relationships also described seeking out those relationships when needed in order to get ‘back on track.’ In Shirley’s experience:

“From time to time I also, if I find me in some sort of crisis, I’ll go and talk to somebody about it, like...a friend. I have lots of friends I can talk to. I proactively [seek out support] when I feel I need it. Like, I know that I need it” (Shirley, age 47).

Spirituality, or having access to a spiritual community, was an important component of social support for a few women. Participants associated faith and spirituality with sustaining hope and motivation in one’s life, regardless of their denomination. As per Tabitha’s experience:

“Being in touch positively affects my life...it is getting in touch with myself through my Creator, right, my higher power. Um, positively affects my life. Um, yeah just believing you know. Yeah, as hard as that can be sometimes, yeah, just believing, hoping, hope, you know. Yeah.” (Tabitha, age 38).

Similarly, faith and prayer was very important to Ursula to maintain a positive attitude, good physical health and control over her HIV. Prayer was not only a time that she could give thanks for good health, it was also a motivating factor to maintain optimal adherence to her antiretroviral medication.

“You know, I actually thank the Lord for this disease... Because it is said, ‘All things, in all things give thanks.’ Because if I didn’t thank Him for it, I would go nuts, literally... Because that gives me strength. It shows that I have power over

disease, the disease don't have the power over me, I have power over the disease. I can't get rid of it on my own though because I need to take the medicine. Every morning that I take those 4 pills out of the box I am usually on my knees because I just say my prayers. And it's a routine that I say my prayers, I read my Bible, I take all those pills" (Ursula, age 57).

For Theresa, praying was associated with feeling 'good inside' and sustaining those feelings throughout the day, even in the face of negativity.

"When I pray, after I pray, I feel really good inside. I forget to do that a lot, especially in the beginning of the day and because I find with praying and it's...it really makes your whole day of thinking negative or positive throughout the day and to try to just obtain that positive thinking throughout the day because a lot of...there is a lot of negativity around" (Theresa, age 42).

Social support was seen as a facilitator to maintaining overall physical and mental well-being because it had a strong influence on women's day-to-day lived experiences and existence. Having access to and utilizing social support enabled women to stay on track mentally and emotionally, as it provided an outlet for reflection and discussion. Faith and spirituality were important sources of support for a few women, as prayer enabled women to reflect on and maintain hope for good physical and mental health. Prayer was also a space where women could privately consider their identity as an HIV-positive woman living with genital herpes.

### *3.6.5. Maintaining boundaries, social roles and engendering HIV*

Participants recognized and expressed the need to set and maintain boundaries in their lives in order to sustain good physical and mental HRQoL. For those women who expressed having good physical and mental HRQoL, the issue of setting and maintaining boundaries was not specific to being HIV-positive, instead, it was related to life demands and social roles assumed. Women had different strategies for asserting and maintaining

boundaries in different relationships, but, for the most part, as articulated by Ellen, it was about finding a balance:

“My mental health... this is at many different levels there because there is, you know, uh, different roles that I play uh, in life...I am a wife, a mother, an employee, a daughter, a sister, a friend and each of those have different, um, stresses...it’s uh, keeping things in balance and uh, not being overwhelmed. I try to deal with uh, with things um, in a healthy way” (Ellen, age 45).

Similarly, Shirley discussed strategies that she had employed for managing and coping with a busy life while ‘trying to meet everybody’s needs.’ Shirley described feeling heightened stress and anxiety from getting herself in situations where she had taken on too much. She understood when she had gotten herself in these situations, and described ways of coping and managing:

“I need extra help at home...now that I am working I am trying to get my house in order...I am on the go constantly, so I try to work from home as much as I can, that helps...Family pressure, my mom wants to see me, my son needs me, and the boyfriend wants to spend time with me, and there is work demands and there is volunteer demands...I just kind of seclude myself for a few days, catch up on things and say, ‘Ok, here I am’...I have taken that time...it’s time for me to do the things I need to do to feel like I am back on track” (Shirley, age 47).

The women welcomed the various life roles that they assumed in their life; although the participants required strategies to manage the various demands of each role assumed, they felt a sense of fulfillment and importance because of their social roles. The roles, therefore, facilitated maintaining good physical and mental HRQoL. For those women who assumed multiple roles, not only was it important to set and maintain boundaries in order to balance various demands, women needed clarity regarding the expectations and nuances of each role assumed. Participants predominantly took on ‘gendered’ roles, that is, roles typically occupied by women, including mothering and care giving, and managed the responsibilities of these roles while managing two chronic viral infections.

One's ability to set and maintain boundaries intersected with their class, race and socioeconomic status, as well as their comfort with and acceptance of their identity as an HIV-positive woman living with genital herpes.

Women voiced the need to set and maintain boundaries in the context of relationships with intimate partners. Shirley related asserting boundaries to asserting one's identity as an HIV-positive woman, as well as assuming different social roles:

“I have sort of developed an attitude where, especially on the relationship aspect, it's like this is who I am, and it's not that I am not willing to compromise, but I am not changing who I am because that will make you happy...I feel really good about that... I have a...complete sort of phase in my life” (Shirley, age 47).

Joni had a similar perspective to Shirley regarding asserting one's identity when setting and maintaining boundaries in relationships. She expressed this perspective in relationship to dating, disclosing one's HIV status and being rejected by potential partners:

“I am looking on the dating sites... get to know them as a friend first and, you know, then once they are my friend, then maybe I will disclose to them that, ‘Oh, by the way,’ you know, ‘I want to be honest with you, I am HIV positive.’ If they kick me to the curb, they kick to the curb, no big deal, but at least I am being honest” (Joni, age 51).

Good physical and mental HRQoL was described by those women who were able to assert their identity as an HIV-positive woman, who held a positive and healthy self-perception and body image, who strove to maintain stability and balance in their day-to-day functioning, and who set and maintained boundaries related to different social roles including intimate relationships.

### 3.6.6. *The choice to “sink”: experiencing poor HRQoL*

An analogy of choosing to ‘sink’ or ‘swim’ was used by one of the participants to describe one’s ability to come to terms with being HIV-positive, and striving to live life with optimal physical and mental HRQoL. There were some aspects of living with two chronic, viral infections that prevented women from being ‘in a good place,’ and, instead, they projected characteristics of poor mental and physical HRQoL including: feelings of uncertainty, episodes of sickness and poor health, fear and anxiety related to their HIV status and insecurity regarding their identity and body image.

### 3.6.7. *Uncertainty about the future and relationships*

One issue that hindered women from maintaining good quality of life was feeling uncertainty and anxiety about their future. Women who described uncertainty about the progression of their HIV disease had made life decisions based on their health status, which, ultimately, affected their perceived HRQoL. Beverly was one participant who made decisions because of her health, and these decisions negatively affected her identity as a woman, her social functioning and her intimate relationships.

“Every decision in my life is affected, um, I make based on my health, it affects every decision...even how I interact with people, so I think that if I didn’t have this disease I would probably have a lot more close relationships. I would make much different decisions in my life...my education path, uh, my career path, my relationship path, even who I married, um, things like that...And not having kids, that’s the biggest one...I thought about doing it for a long time but then I’d, see even that decision, is what if I go into this child’s life and then I get sick and die? How is that going to affect a kid, she doesn’t have a mother...you do judge, or make your decisions on, uh, just not knowing if you’re going to be here tomorrow” (Beverly, age 42).

Beverly’s narrative demonstrates the toll that living with two chronic, viral infections, especially HIV, can have on decision-making and planning for the future. The fear of

uncertainty plagued Beverly; her diagnoses had determined her life journey. Beverly most poignantly described this uncertainty in her decision not to have children, which, for her, was a very difficult one.

Participants also related feelings of uncertainty and anxiety to reframing their lives and futures after receiving their HIV diagnosis. For Ursula:

“I figure I got to live the best I can, and just take it one day at a time...the disease made me realize that life is not a 100 years from now, life is today, and I have to take every day as it comes and realize, I can go to sleep and fall off into eternity, and not enjoy it, because I am not thinking of today, I am thinking of years down the line, and so I had to re-evaluate my life once this illness come on me...I have to be strong for my family and for my friends...my clients and just keep on living one day at a time now and be thankful every morning I wake up” (Ursula, age 57).

Similarly for Joni, quality of life:

“Means looking into the future which I have done, I have already thought about my future. Nobody knows how long they are going to live...I have put away for my future. I have got my pension... hopefully I will stay healthy, knock on wood, the rest of my life and look after myself...What? I am going to wait till I am 65 till I retire before I travel? I might be dead by then. I have to travel now. I have to enjoy life. Enjoy life to the fullest every day” (Joni, age 51).

After receiving their HIV diagnoses, Ursula and Joni came to the realization that they could not control the uncertainty that they were feeling about their future. Although they both described themselves as women who preferred to plan ahead and have an idea as to what their future may look like, HIV had required them to reframe and adjust their way of living; they now lived life one day at a time. Although the women described accepting this new way of thinking and living, they still considered this a challenge to their mental HRQoL.

Because of the inconsistency in the presentation of genital herpes symptoms, women expressed uncertainty regarding the acquisition and transmission of HSV-2. Not knowing from who they had acquired HSV-2 infection and being with partners who did



not have any genital herpes symptoms caused strain in relationships and made women question the honesty and trust they shared with partners. As in Theresa's experience:

“I said to him, like, ‘I could have had it for a long time or I could have gotten it from you. You don't even know you have it...because you never had an outbreak’... this is the argument or fights I... honestly had with my husband” (Theresa, age 42).

The uncertainty of acquisition and transmission of STVIs was conveyed more strongly for herpes and other physically manifesting STVIs including HPV than for acquisition and transmission of HIV. Women communicated an understanding of the typical reliance on symptom onset for diagnosing HSV-2 and HPV, rather than a blood test, which is used to definitively confirm and diagnose HIV infection.

### *3.6.8. The physical is linked to the mental*

Episodes of sickness and poor physical health negatively affected women's physical and mental HRQoL. For some women, the acute, poor physical health that they experienced was attributed more to genital herpes outbreaks than to HIV infection. In Beverly's case, the herpes outbreaks caused pain and fatigue.

“When I have a herpes outbreak, I can, for a couple of days before it, before I realize, I'll feel really, um, extraordinary pain, uh, tired... You get really emotional with it because you just, it drains you and you're upset and you're uncomfortable. And it affects my working out, if anything affects my working out it pisses me off” (Beverly, age 42).

For Beverly, herpes outbreaks were first associated with a physical response of pain and fatigue followed by an emotional response of frustration and upset because of the impact the outbreaks had on her day-to-day functioning and her ability to live a 'normal' life, for example, maintaining an exercise schedule. Conversely, Shirley attributed her episodes of fatigue to all of her medical conditions:

“The hardest one to work through is fatigue, which I think is related to HIV, arthritis, herpes, related to all of the things that I am dealing with in my life, and that’s the hardest one because you can’t make the time back and if you’re exhausted, you’re exhausted, and there is not really much you can do about it, so I find that kind of frustrating” (Shirley, age 47).

Shirley also described having an emotional response such as frustration because of a physical health threat. Her narrative highlights the frustration that many HIV-positive women experience in not only living with and managing two chronic viral infections, but also managing other co-morbid health conditions such as arthritis, and how this can impact one’s HRQoL.

### *3.6.9. Fear*

Fear was another important theme that women described having a negative affect on perceived physical and mental HRQoL. The fear that women described was in relationship to potentially transmitting their HSV-2 and HIV infections to intimate partners, as well as disclosing their HIV status to partners, family and friends, and experiencing rejection and judgment as a result. As stated by Ursula:

“There is no way I could see me telling a man, ‘Look at here, I have HIV and herpes, so you have to use a condom to be intimate with me.’ I don’t see me ever be able to tell that to a man, I can’t see it. I have been, I treat myself with respect and dignity all my life and this still happened to me, so, it’s kind of, ‘Oh my goodness!’ They gonna...I mean, they would look down on me, they will walk away from me and I am gonna lose friends, I lose my friends and I can’t do that, I cannot afford to” (Ursula, age 57).

Ursula had made the decision not to enter into new, intimate relationships with men. She understood the obligation to disclose her HIV status to sexual partners, but, because of her fear of being rejected and losing friendships, she decided that it was not worth it. Instead, she had made the decision to concentrate on her work, her grandchildren and her

faith, all of which were positive influences on her mental HRQoL. Ursula's ethnicity as a Black woman from the Caribbean, her social class, and her socialization and upbringing in a faith-based home intersected with her fear of disclosure and experiencing rejection and judgment.

Similarly, Ellen described a fear of being 'outed' and losing control over who in her life was aware of her HIV status, resulting in rejection and judgment by family and friends:

"I think probably the biggest affect is um, you know, there is the fear of um, word getting out and it's just not something that uh, I want to happen...Because there is still so much uh, there is still so many wrong, uh, thoughts, concepts, and you know, people just assume the worst. Uh, so I think that's uh, that's always on my mind" (Ellen, age 45).

Although Ellen described having stability and control over who was aware of her HIV status, she still expressed fear of losing this control and being 'found out.' This balancing act of maintaining, yet potentially losing, this control had a negative affect on Ellen's mental HRQoL. Fear of transmission of HIV and/or HSV-2 infections to intimate partners was closely linked to the fear of rejection and being 'outed' as described by Beverly:

"I think with the combination of herpes and HIV, that the big thing is being judged and passing it on, that's the big thing...I would rather die than pass it on to somebody" (Beverly, age 42).

Fear was an important theme that women linked to living with HIV and genital herpes. Fear of passing HIV and/or HSV-2 to sexual partners, fear of being 'outed' as an HIV-positive woman living with genital herpes, and fear of being rejected by sexual partners, family and friends resulted in negative perceived mental HRQoL.

### 3.6.10. *Negative perceptions of self and body image*

Rather than asserting one's identity as an HIV-positive woman living with herpes, some women expressed insecurity about their perception of self and their body image; this theme had a negative influence on their overall physical and mental HRQoL. Women attributed negative perceptions of their body to having genital herpes more so than living with HIV because of the physical manifestation of their herpes outbreaks. When asked about how physically manifesting STVIs were different than HIV, Theresa described the tangible nature of STVIs, specifically herpes and HPV, which she had had problems with:

“More of the herpes and HPV than the HIV, yeah, because it's right there in my face. It's right, it's there, you know...I can feel that. It's tangible. It hurts there. HIV is not tangible. You can't feel it. You can't see it” (Theresa, age 42).

Shirley echoed Theresa's narrative regarding the physical manifestation of herpes, expressing discomfort with herself and her body, even though she had been living with HIV and genital herpes for almost 20 years. Shirley aligned these negative perceptions of her body with how she may be perceived by potential partners.

“It could possibly make me less attractive to someone. I mean, not physically less attractive, but it could, I think it could impact potentially getting involved with somebody...Recently I started thinking about that, like, ‘Oh, man, like, you know, that's just another thing I have to say’...What does that say about me as a person? Like, does it mean, like I wasn't careful, or people are gonna think, like, I am a disease or walking infection or, you know, like, I don't feel good about it. It doesn't feel good...Herpes is different. I don't know, I think because you can see it...It's only related to sexual activity. It's not like, you could not have got it from some other means. So, I am just feeling like diseased. Like, I just feel diseased!” (Shirley, age 47).

For Shirley, genital herpes was associated with deviance and it elicited negative perceptions of self and body image. She compared HSV-2 infection, which could only have been acquired sexually, and herpes outbreaks, which could be seen and felt, to HIV,

which could have been acquired via non-sexual behaviours including injection drug use or non-deviant behaviours including receipt of tainted blood products or vertical transmission. The physical manifestation of HSV-2 infection and its association with deviant sexual behaviours not only made women question their perception of self and their body image, it subsequently interfered with their ability to be intimate with sexual partners. The negative affect of HSV-2 on self-perception and body image highlights the uniquely gendered nature of HSV-2 compared to HIV. The physical manifestation of HSV-2 was associated with women feeling ‘dirty’ and ‘diseased’, which negatively influenced their ability to take on and fulfill social roles as intimate partners and sexual beings. Overall, this had a negative affect on their perceived physical and mental HRQoL.

Negative perceptions of body image also came out in women’s narratives that described a desire to control one’s body. The body was considered something that women could control in the chaos of living with two chronic STVIs. In Beverly’s case:

“I compensate by, uh, you know, working out so much and taking care of my body and having, uh, so the things that I control, I go extreme. Like I’ll, I can’t just go for a run, I have to run a marathon. I can’t just work out, I have to be in fitness competitions and win them. I can’t just, um, be good at my job, I have to win awards. Um, so with the herpes, that’s something I can’t take cont-, I can’t control. Um, that affects me... I try to gain my self-esteem and make up for it in the other areas because, um, yeah, I just, I almost don’t like myself (Beverly, age 42).”

Even though Beverly was a physically fit and athletic woman, her narrative projected a negative perception of her body. For Beverly, working out was not equated with beauty, rather it was associated with control, perfection and compensation because of low self-esteem and self-confidence. When Beverly was sharing her need to physically control her

body, she also described an emotional need to control by rejecting her reality of living with HIV and herpes:

“I live my life as if I’m not HIV-positive or as if I’m not herpes and I just, I don’t think about it, I just deal with it. Cause it’s times when I talk about it...I’m crying my eyes out...I try to live as normal as I can and not, and not even have it part of my day...When I’m sick or when I have an outbreak that you can’t ignore it, it’s there, it’s calling your name and so that pisses me off” (Beverly, age 42).

Beverly’s story highlights the stigma and marginalization that women may experience if they are living with two chronic STVIs. On the outside and to the people around her, Beverly’s medical conditions were not visible and she had chosen to tell minimal people in her life. Beverly lived her life ‘passing,’ as if she was a woman who did not have HIV or herpes; Goffman comments that ‘passing’ is one way that individuals control and keep hidden their personal identity when stigma or rejection are feared or assumed.<sup>160</sup>

Similar to Beverly’s narrative of the need to have physical and emotional control over one’s body, Ursula highlighted a need to stronghold her identity as a woman. Ursula’s experiences of abuse and mistreatment in relationships were a catalyst for projecting, what appeared to be, a strong, feminist identity. This projection, however, was out of necessity to defend one’s honour and dignity in the face of oppressive and abusive relationships.

“I got married when I was 20, and I thought I got my soulmate...I thought when I got married, I was going to have the same kind of life and it didn't happen, so I was very disappointed...When I got sick, basically, water ruptured after delivery from the second pregnancy, and he got himself a girlfriend. But he did have her before but I didn't know because the way I was raised, you say ‘I do,’ so you stick with your wife...I just basically went to work, went to church and take care of my family...you just behave yourself as a woman then. My sister said I should try and say, ‘I am a lady,’ but I am not a lady, I am a woman. That means I can be loveable, my bark is worse than my bite but if you mess with me I can, you know, put you down. So, physically, I mean, you know what I mean, or with my mouth, or with my eyes” (Ursula, age 57).

Another way the women illustrated a negative self-perception and body image was in potentially being the one who brought a physically manifesting STVI into a relationship; this fear had a negative affect on women's mental HRQoL. Because of a lack of certainty of who infected who with HSV-2 and/or HPV, but being the one in a relationship who had symptomatic STVIs compared to her partner, Theresa described feeling 'sub-standard' and projected a negative self-perception and body image:

"It hurts me. It's hard to deal with that...I wanted to change the subject with him, you know, I don't want to talk about it. It's embarrassing. I feel embarrassed. I feel embarrassed and I feel dirty. I feel really dirty" (Theresa, age 42).

This negative self-perception impacted Theresa's comfort and ability to be intimate with her husband:

"I don't want to have sex...He wants to go down on me...I am just like, 'No! I don't even want you to go down on me because I still feel like dirty down there'" (Theresa, age 42).

For many women, living with HIV and genital herpes had negative connotations. These two chronic STVIs were the catalyst to women feeling uncertain and insecure about their identities, their bodies and their relationships with others. Both infections were the source of episodes of sickness and poor physical and mental health. Finally, living with HIV and herpes caused women to experience fear and anxiety of being 'outed,' rejected and judged by their peers, by friends, by family and by partners. Beverly articulated all of these negative connotations when she described her experience:

"Living with combined is, it's like a double, um, attack on your, on your pride and on your self-esteem because if it's, if you could just go into a relationship and you have to tell them that you have one thing but you have to tell him that you have two things. And, um, people are scared and I don't blame them. Uh, but it does, it does, like again, both, both make you feel like you're a dirty person. And, I'm a very proud person so, um, I choose not to tell anybody about that" (Beverly, age 42).

### *3.6.11. Overall HRQoL in women co-infected with HSV-2 and HIV*

With regard to maintaining good physical and mental HRQoL, women referenced being able to assert with confidence their identities as HIV-positive women, and maintaining a positive self-perception and body image. Having and maintaining stability in life was another important factor to ensuring good HRQoL. Stability included medical stability through treatment regimens for HIV and HSV-2 and stability and control over one's HIV status, such as who was aware of that status. Access to and utilization of supportive and fulfilling relationships was important for women to stay in a 'good place'; social support, faith and spiritual communities facilitated this. Finally, setting and maintaining boundaries around one's identity as an HIV-positive woman living with herpes and in relationships with others was a positive influence on women's perceived physical and mental HRQoL.

There were a number of themes that women associated with poor or negative HRQoL, as they inhibited women to be and stay in a 'good place.' These themes included feelings of uncertainty regarding one's future and life expectancy, especially after receiving an HIV diagnosis. Women also expressed uncertainty regarding the acquisition and transmission of HSV-2 in relationships; not being sure who had infected who with HSV-2 and the inconsistency of presentation of genital herpes symptoms caused strain and anxiety in relationships with partners. Having episodes of sickness and poor health negatively affected both physical and mental HRQoL. An example of this was pain and fatigue caused by genital herpes outbreaks, which lowered women's perceived physical and mental health because of its impact on day-to-day functioning, being able to assume different social roles and living a 'normal' life. Fear of being rejected after disclosing



one's HIV status and fear of being 'outed' or found out were themes that predominantly affected women's mental HRQoL in a negative way. Fear, however, was a construct that also impacted women's physical health because of the bodily response that ensued.

Finally, some women described negative perceptions of self and their bodies, which had an overall negative affect on their perceived physical and mental HRQoL.

Although women spoke of ways in which genital herpes affected perceptions of their mental and physical health and subsequent quality of life, in the grand scheme of things, HSV-2 infection and genital herpes was not their primary concern. Genital herpes was viewed differently than HIV; it was an 'issue' that they were managing in their life in addition to their HIV. Genital herpes was not something that predominantly dictated their global HRQoL, instead, it was a concern that presented itself and that they had to deal with on an episodic basis, for example, when they were experiencing a herpes outbreak. HSV-2 was also presented as a 'gendered issue' as it particularly affected the perceived physical and mental HRQoL of women. HSV-2 infection influenced women's abilities to assume social roles including caregivers, mothers, and sexual beings, and influenced their perceptions of self and body images differently than HIV.

Ultimately, women associated overall good quality of life with maintaining a balance and having their needs fulfilled, which they were responsible for as agents of change and action. As stated by Shirley:

“Quality of life is being able to achieve whatever you have set up for yourself, and to be able to do it without, or with as little stress and anxiety as possible...I think in the overall big picture of my life that this herpes is, that herpes isn't gonna make a big difference” (Shirley, age 47).

Similarly, as highlighted by Ursula:

“Quality of life would be, uh, living without fear, living without pain, having food to eat and having enough, whether it’s food or clothing, to share with other people, to me that’s quality of life” (Ursula, age 57).

Finally, Ellen experienced ‘quality of life’ as:

“The ability of live life, function in life...I do have a, a good quality of life in that I can enjoy my life, I make my own choices, handle my own business, my own affairs...Being in a good place, I am, you know, being relatively healthy, being able to function and, um, you know, care for the children, care for the house, uh, go to work everyday, those kind of things, um, being able to sense enjoyment” (Ellen, age 45).

### **3.7. Discussion**

The participant narratives highlighted how women uniquely experience HIV and HSV-2 infections, as well as what meaning they ascribe to living with both chronic STVIs in relationship to their perceived HRQoL. HIV was something that affected their global physical and mental HRQoL because it was associated with a social and historical context and was mapped onto their life trajectories. HSV-2, on the other hand, was an immediate concern experienced on an episodic basis, therefore was more relevant to dimensions of HRQoL such as day-to-day physical and social functioning, as well as intimacy and relationships with partners. Women talked about HSV-2/HIV co-infection as a gendered issue because of how it affected their ability to navigate social and sexual relationships, as well as assume social roles typical of women including mothers, caregivers and intimate partners. A number of themes were described, which enabled women to overcome their diagnoses and move forward with their lives, achieving good or positive physical and mental HRQoL. There were also a number of themes that prevented or impeded women from achieving good HRQoL including experiences of HIV-related stigma, having uncertainty about their futures and relationships, experiencing poor

physical health, experiencing fear and maintaining a negative self-perception and body image because of their co-infections. One overarching theme that all women described was the journey towards acceptance and understanding of their diagnoses; each participant was at a different stage of this journey. Some women described having agency and responsibility for their co-infections, regardless of any HIV-associated stigma that they may have witnessed along the way. The women who had reached a point of acceptance, understanding and responsibility on the whole described good day-to-day and global HRQoL.

It is clear from the qualitative findings that HSV-2 infection is a separate and dominant medical condition that compounds and complicates a woman's experience with HIV. It would be important for service providers including clinicians, social workers, and support workers at community-based organizations to account for HSV-2 as an important medical and psychosocial issue and to discuss with their clients how HSV-2 may relate to or affect a woman's perceived HRQoL. No quantitative or qualitative research, or mixed methods research for that matter, have explored the relationship between HSV-2/HIV co-infection and HRQoL in adult women. It is an important area of development for theoretical and applied knowledge, especially as women continue to live chronically with HIV/AIDS. This study adds to the body of knowledge regarding women's experiences living with HIV, but adds an important layer regarding co-infections and co-morbidities, which are relevant to developing models of understanding in women's sexual health.

As constructs, physical and mental HRQoL were inextricably linked. Threats to physical health, for example, pain and fatigue caused by genital herpes outbreaks, elicited

emotional and psychological responses, thereby negatively affecting mental HRQoL. Episodes of pain and fatigue heightened stress and anxiety by preventing women from accomplishing daily tasks and fulfilling social roles. Similarly, threats to mental health, for example, fear of being ‘outed’ or found out as a person living with HIV and HSV-2, resulted in physical symptoms, including anxiety and nervousness. Maintaining optimal HRQoL rested on one’s ability to cope, manage, balance and respond to life challenges with resilience and acceptance.

The ‘physical body’ and the ‘embodiment’ of the person in their environment were important constructs in understanding women’s meaning and narratives about their physical and mental HRQoL in relationship to living with two chronic STVIs. Saleeby describes the complex and dynamic interaction between the mind, body and environment and how one’s perspective and social construction of disease are relevant to this dynamic.<sup>161</sup> Saleeby attributes the process of recovery and transformation when managing a disease to beliefs held about oneself, including beliefs about the body and elements of the environment in which those beliefs arise and are sustained. The social constructivist theoretical paradigm articulated by Charmaz highlights hierarchies of power, social interactions and complexities of local worlds; views and actions are significant to understanding one’s reality.<sup>142,144,147</sup> Similarly, Saleeby and Zegans describe an undermining of one’s sense ‘of competence, identity, status and power’ when confronting a dramatic, noticeable change in their body because of a physical experience such as aging, disability, disease or trauma, including HIV and symptomatic genital herpes infection.<sup>161,162</sup> Receiving such diagnoses and being left with the choice to ‘sink’ or ‘swim’ resulted in ‘the feeling of groundedness and ease in negotiating the world of

objects and people' for many of the women who were interviewed for this study. Saleeby offers that 'the path to liberation frequently begins by helping individuals reclaim the sense of their body, along with its potentials, energies, and peculiarities.'<sup>161</sup> In the case of the participants living with HIV and symptomatic HSV-2 co-infections, those women who expressed agency and responsibility for their medical conditions asserted a more positive physical and mental HRQoL compared to those women who expressed regret and a more negative physical and mental HRQoL. The assertion of agency and responsibility enabled women to reclaim their bodies and identities as HIV-positive women living with genital herpes.

Women recounted their experiences of living with HIV and symptomatic HSV-2 co-infections to me as a researcher and as someone interested in understanding the meaning that they ascribed to living with these infections. How women described themselves and depicted their lives was dependent not only on how much they had reclaimed their bodies and their environments as per Saleeby,<sup>161</sup> but also on who their audience was and the context in which they were sharing. The creation of their self images and stories were grounded within, and reproduced by, their context and discourse of social responsibility.<sup>163</sup>

Goffman describes how having a 'spoiled identity' and experiencing stigma because of stigmatizing illnesses such as HIV and genital herpes can impact a person's ability to 'perform' and 'pass' in life.<sup>160</sup> For many women, their identity as an HIV-positive woman living with genital herpes was constructed not only by their social and historical contexts, but also by any exhibition of stigma, fear and ignorance they had witnessed in their lives. In certain contexts, women lead double-lives 'passing' as

‘normal’ women as if they were not living with two chronic STVIs. Women chose to ‘pass’ and keep the reality of their illnesses hidden from family members, friends, co-workers, and new relationships that were not yet of a sexual nature, however, their illnesses influenced how they engaged in all of these relationships. For example, Ursula and Joni referenced being more aware of and stringent with employing universal precautions with clients at work, not only to protect clients, but also to protect themselves.

Women’s abilities and desires to ‘pass’ may have been influenced by their cultural contexts and their perspectives of claiming their ‘physical bodies.’ According to Saleeby<sup>161</sup> and Corea,<sup>164</sup> asserting ownership over one’s body, particularly for women, is culturally very difficult. First, females may not be socialized to the reality and possibility of their physical bodies,<sup>164</sup> as was voiced in Ursula’s description of her upbringing. Second, women may have the views of others regarding physical bodies, sexuality, morality and deviance imposed on them, with the result that they come to regard female sensuousness as deviant, ‘suspect’ and ‘disreputable.’<sup>164</sup> Overall, women’s abilities to assert authority and ownership over ‘sensuous power and bodily energy,’ as well as to assert and disclose their identities as HIV-positive women living with genital herpes, have been ‘thwarted and oppressed.’<sup>161,164</sup> Women have been charged with the task to self-‘govern’ their ‘contagious bodies;’<sup>166</sup> and this reality was eloquently expressed in women’s narratives and storytelling. As summarized by Foucault, “the presentation of self is a moral enterprise, with the confession a core aspect of self-discipline.”<sup>163,165</sup>

Oster and Cheek utilized a theoretical framework proposed by Foucault based on the theorization of governmentality in order to qualitatively explore the ‘technologies of

the self' by which people living with genital herpes, who were not HIV-positive, governed their 'contagious' bodies.<sup>166</sup> According to Foucault, 'technologies of the self' are those practices and techniques "which permit individuals to effect by their own means or with the help of others a certain number of operations on their own bodies and souls, thoughts, conduct and ways of being, so as to transform themselves in order to attain a certain state of happiness, purity, wisdom, perfection or immortality."<sup>166,167</sup> Oster and Cheek found that regulation of the 'contagious body' was an ongoing ethical dilemma for people with genital herpes. Two 'technologies of the self' were identified as being employed by people living with genital herpes, namely the self-discipline of 'irresponsible sexuality' through the prioritization of the risky self, and the engagement in 'irresponsible sexuality' through the prioritization of the at-risk self. Participants interviewed by Oster and Cheek expressed a need to ethically govern themselves and to be 'responsible managers' of their illness, particularly with regard to sexual risk and disclosure to sexual partners. Understanding the 'technologies of the self' by which people living with genital herpes were 'governed' enabled a more comprehensive and broader understanding of the management and self-regulation of chronic illness, including genital herpes in the context of HIV co-infection. Returning to Foucault's definition of 'technologies of the self' and relating the construct of self-'governance' to the group of women interviewed for this thesis, how women living with both HIV and genital herpes 'be in the world' and 'govern,' manage, and assert their identities and bodies directly affects their subsequent perceived physical and mental HRQoL.

### ***3.7.1. Validity and trustworthiness of the qualitative analysis and interpretation***

As stated by Sandelowski, “engagement with rather than detachment from the things to be known is sought in the interests of truth.”<sup>170</sup> As such, it was important to engage with study participants in a subjective manner, rather than with objective detachment.<sup>171</sup> This subjective engagement enabled the meanings that women ascribed to and derived from their life experiences to be emphasized; the presenting themes were grounded in their voices and the description of their experiences was valued throughout this qualitative phase.

The women who were interviewed for this interpretive phenomenological study were considered appropriate to represent women’s unique experiences living with symptomatic HSV-2 and HIV co-infections. It should be cautioned, however, that this qualitative analysis predominantly encapsulated the subjective and unique experiences of Canadian-born, Caucasian women with the exception of one woman who identified as Black Caribbean and another who identified as Canadian-born Aboriginal. The voices and experiences of some women, therefore, were not represented or explored in this study; and the subjective meanings that were discussed may not be true for women who identify with other ethnicities, cultural backgrounds, age groups or social classes. The lack of representation of some groups of women may have resulted in an ‘elite bias,’ that is, the study participants may have been more articulate, accessible or high-status members of their social groups.<sup>172</sup> Of the three women who declined to participate in an interview, all were non-Canadian-born; two of the women identified as Black African and the third was of Hispanic ethnicity. The three women who did not agree to participate



seemed reluctant and uncomfortable discussing their personal experiences when they were approached for the study.

## **Chapter 4**

### **Conclusions and reflections regarding the synthesis of quantitative and qualitative findings in a mixed-methods study**

The overall purpose of this mixed methods study was to explore the association between HIV and HSV-2 co-infection and physical and mental HRQoL of adult HIV-positive women. A sequential exploratory model was utilized whereby qualitative data was collected and analyzed after a quantitative phase; different sources of data were important to corroborate, validate and comprehensively understand the research questions of interest. In the first cross-sectional, quantitative phase, HSV-2 serology was completed and women were asked to fill out self-report demographic and HRQoL questionnaires. The quantitative data was analyzed using univariable and multivariable methods in order to provide a general understanding of the statistical associations between HIV/ HSV-2 co-infection and HRQoL. The second qualitative phase was conducted in order to refine and further explain the quantitative associations, and to explore in greater depth and from the perspective of participants' the relationship between symptomatic HSV-2/ HIV co-infection and HRQoL.<sup>123,124</sup> Interpretive phenomenology philosophy and methodology informed the qualitative phase. The following mixed methods research question can now be answered: How did women's narratives outlining their perceptions and experiences of living with HIV and HSV-2 explain the quantitative relationship between HIV/HSV-2 co-infection and physical and mental HRQoL?

Univariable analyses in the quantitative phase found that HSV-2/HIV co-infected women had significantly higher physical and mental HRQoL as measured by the MOS-HIV compared to women infected with HIV alone; co-infected women had an almost 6-

point higher PHS and a 7-point higher MHS compared to HSV-2 negative, HIV-positive women. The SF-12v2, on the other hand, indicated that HSV-2/HIV co-infected women had a similar PHS to HSV-2 negative, HIV-positive women; and, co-infected women had a 2-point higher MHS compared to women infected with HIV alone. Both the PHS and MHS SF-12v2 scores were not significantly different between groups in the univariable analysis. It did not seem biologically plausible that HSV-2 infection would be associated with an increase in either the PHS or MHS compared to mono-infection with HIV. The argument was made that other contextual factors were confounding or modifying the relationship between HSV-2/HIV co-infection and HRQoL. Linear regression modeling was then employed to investigate the potential confounding or effect modifying variables; regression modeling highlighted the modifying effect of place of origin on the relationship between HSV-2 sero-status and PHS or MHS. Overall, it was concluded that although women's HRQoL scores on the MOS-HIV or SF-12v2 differed depending on their HSV-2 sero-status, place of origin, receipt of HAART, etc., HSV-2/HIV co-infected women did not have significantly different HRQoL scores compared to women infected with HIV alone. This conclusion was drawn on the basis of only fair goodness-of-fit of the linear regression models determined by the adjusted R square values, the statistical significance of the unstandardized beta coefficients in all four models as well as the biological implausibility and divergence with the literature that HSV-2 sero-positivity would predict a better perceived physical and mental HRQoL. It was also noted that other contextual factors that were not captured in the regression modeling, for example, education, income, and other social determinants of health, were most likely confounding or modifying the relationship between HSV-2/HIV co-infection and HRQoL, which had a

positive influence on the statistical relationship between HSV-2/HIV co-infection and HRQoL.

The statistical differences in physical and mental HRQoL scores between the MOS-HIV and SF-12v2 may have also been partly attributed to the specific dimensions measured or captured by these HRQoL questionnaires. The MOS-HIV captures ten dimensions of HRQoL in 35-items including general health perceptions, bodily pain, physical functioning, role functioning, social functioning, mental health, energy/vitality, health distress, cognitive functioning, and health transition. The SF-12v2, which was derived from the generic SF-36, reflects 8 sub-domains including physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. The constructs of health distress, cognitive functioning and health transition are not captured, but may be important for HIV/HSV-2 co-infected women's overall HRQoL.

Interpretive phenomenological methodology employed in the qualitative phase enabled an in-depth exploration of HIV-positive adult women's experiences living with symptomatic HSV-2 infection. Women's narratives highlighted how living with genital herpes affected their perceived physical and mental HRQoL by creating disruptions and fluctuations in the dynamic between 'being' and 'not being' in a 'good place.' Themes that facilitated maintaining good physical and mental HRQoL included: having agency and asserting one's identity as an HIV-positive woman; having a positive self-perception and body image; maintaining medical and social stability; having access to and utilizing social and spiritual support; and setting and maintaining boundaries. Themes that were associated with poor or negative HRQoL included: feelings and experiences of

uncertainty and fear; having episodes of sickness and poor health; and having a negative self-perception and body image. Although women spoke of ways in which genital herpes affected perceptions of their physical and mental health and subsequent quality of life, in the grand scheme of things, HSV-2 infection and genital herpes was not their primary concern. Genital herpes was viewed differently than HIV; it was an 'issue' that they were managing in their life in addition to their HIV. Genital herpes was not something that predominantly dictated their global HRQoL, instead, it was a concern that presented itself and that they had to deal with on an episodic basis, for example, when they were experiencing a herpes outbreak.

Taken together, the quantitative and qualitative findings suggest that HSV-2 infection and subsequent genital herpes outbreaks is a construct that influences HIV-positive women's overall perceived physical and mental HRQoL because of its influence on different dimensions of HRQoL including physical function and symptoms, performance of social roles and social well-being, and psychological or emotional status.<sup>2-4</sup> HSV-2 infection was one of many factors for HIV-positive women that tipped the balance between having good perceived quality of life, or, being in a 'good place' and not having good perceived quality of life. To what degree HSV-2 infection manipulated the dimensions of HRQoL in HIV-positive women depended on whether their HSV-2 infection was symptomatic, where they were at in their journey of acceptance and management of the HSV-2 and HIV infections and what other life challenges they were dealing with, for example, co-morbid physical and mental health conditions and unmet needs pertaining to the social determinants of health.

The model of needs fulfillment that is employed when numerically measuring HRQoL is also relevant to women's qualitative phenomenology. For example, the Recurrent Genital Herpes Quality of Life questionnaire is based on the premise that "life gains its quality from the ability and capacity of the individual to satisfy his or her needs."<sup>3</sup> Quantitatively, when HRQoL scores are high, needs are fulfilled, whereas when HRQoL scores are low, few needs have been satisfied. This conceptual framework aligns with the narratives of HIV-positive women with symptomatic HSV-2 infection that were explored during the qualitative phase. Good or positive HRQoL was associated with need fulfillment in women's relationships with themselves and their bodies, as well as with friends, family, co-workers, and partners. Need fulfillment was also expressed in regard to maintaining medical and social stability, social and spiritual support, and boundaries in relationships. Poor or negative HRQoL, on the other hand, was associated with a lack of need fulfillment in regard to women's relationship with themselves and their bodies, an inability to live life without fear and uncertainty their futures and relationships with others and an inability to always maintain optimal physical and mental health due to their underlying health conditions.

The population included in the quantitative, cross-sectional analysis were women, many of whom were relying on social assistance and/or governmental benefits as their primary source of income. The MOS-HIV has had relatively little use in research studies involving women, people with lower socioeconomic status and injection drug users,<sup>14</sup> therefore the ability and trustworthiness of the MOS-HIV to accurately measure and reflect perceived HRQoL in this group of HIV-positive women co-infected with HSV-2 infection must be called into question. The needs of HIV-positive women co-infected

with HSV-2 and perhaps other chronic, viral infections such as HPV or Hepatitis C may be different than the groups of HIV-positive individuals who were involved in the development of these HRQoL measures, i.e. men who have sex with men. For example, the MOS-HIV does not include some general aspects of HRQoL including sleep patterns, eating habits and sexual functioning,<sup>13,14</sup> which were relevant constructs expressed by women who participated in the qualitative phase. Other needs that were important to HIV-positive women co-infected with HSV-2 that were expressed qualitatively were acceptance by friends and family and support of peers, not experiencing fear of rejection when disclosing their HIV and herpes status to partners, and having a sense of fulfillment in their employment, family lives and relationships.

Conceptual models of illness self-regulation and adaptation are important when attempting to comprehensively understand the quantitative, statistical and qualitative, phenomenological relationship between HIV/HSV-2 co-infection and perceived HRQoL in women. These models are grounded in constructs that are important to and generated by participants involved in their development and focus on the process of self-regulation in acting to prevent, treat, cure or adjust to an acute or chronic illness.<sup>182,183</sup> All models of illness self-regulation are based on the following three fundamental themes: (1) Individuals are self-regulating systems, that is, they are active problem solvers who try to make sense of potential or existent changes in their somatic state and act to avoid or control those changes perceived as signs of illness or physical disorder; (2) Individual's understanding and skills form one's common sense beliefs and appraisals, which form the basis of the process of adaptation; and (3) The role of the sociocultural environment is important and emphasized in shaping the self-regulation process, that is, individuals

represent and cope with health issues based on their perceptions, or representation, of the attitudes and beliefs of their social and cultural environment.<sup>182</sup> The ‘common sense model’ of illness self-regulation emphasizes the subjective nature of the disease experience assuming that individuals construct meaning for illness and disease using an information-processing approach, which occurs in three stages: representation, coping and appraisal.<sup>182,183</sup> The process of illness self-regulation is linear. Internal and external stimuli generate the cognitive self-representation of illness and emotional reactions, which guide the coping process of selecting and executing coping responses. Selection of the coping process is followed by appraisal where individuals evaluate the effectiveness of coping activities and potentially alter their illness representation and the coping strategy employed.<sup>182</sup> Overall, the process and construction of illness self-representation, the selection and execution of coping strategies and their subsequent impact on affective processes is a dynamic one, for example, representations of illness and the resultant self-regulation may change over time as a disease progresses or evolves.

Illness self-representation is influenced by a number of concrete and abstract factors. Individuals derive meaning from interactions with the ‘concrete’ self, that is, the ‘working’ or ‘functional’ self.<sup>182</sup> The ‘concrete’ self may be understood as one’s symptomatic identity of disease or anticipated symptoms of disease and treatment such as energy to complete or adhere to treatment and one’s perceived ability to tolerate pain and injury associated with the disease and its treatment. The ‘abstract’ self includes one’s beliefs about life expectancy and health uncertainty, which interact with higher order factors of the self-system such as optimism-pessimism, feelings of vulnerability to harm, and self-efficacy in adhering to treatment regimens.<sup>182</sup> Overall, the combination of the



'concrete' and 'abstract' selves in the self-representation of illness is nested within broader personal, social and cultural contexts. How individuals choose to represent their symptoms is influenced by their life experiences, institutional, systemic, cultural and community affiliations and roles assumed, for example, their perceived identity, causes, time lines, consequences and control, as well as the affective reactions that symptoms evoke, and strategies that are used to manage symptoms.<sup>182</sup> Self-representation of illness is then influenced by factors that extend beyond the individual including social norms, media representations of illness and societal discussions of the causes and consequences of illness.<sup>182</sup>

HIV-positive women co-infected with HSV-2 defined their illness and their resultant HRQoL in accordance with Leventhal, Leventhal and Cameron's self-regulation of illness model (Figure 1). First, HIV/HSV-2 co-infection was represented from the perspective of their phenomenal reality, that is, illness experience was represented in terms of an identity (i.e. the symptoms or labels that define it), time line, consequences (i.e. physical, emotional, social and economic outcomes), cause and controllability (i.e. the anticipated and perceived responsiveness of the condition to self-treatment and expert intervention).<sup>182</sup> Second, illness was represented as an emotional reaction where feelings of distress, fear, anger, etc. were elicited. In other words, HIV-positive women living with HSV-2 infection processed information to control their underlying physical health issues and to control emotional responses elicited by their physical health issues.

#### ***4.1. Implications for practice***

The synthesis of quantitative and qualitative findings describing the relationship between HIV/HSV-2 co-infection and HRQoL, as well as the conceptual model of illness self-regulation offer important implications for practice and service delivery. When engaging women to self-regulate and manage their HIV and HSV-2 co-infections as a service provider, it is optimal to engage in ‘embodied practice.’<sup>168</sup> To engage in ‘embodied practice’ is to claim the body’s experience, agency and knowledge, and to take into consideration the multidimensionality of the body in practice and service provision as clinicians, social workers or community-based service providers. The multidimensionality of the body includes: (1) the ‘experiencing body’ is focused on the physicality of daily life; (2) the ‘body of power’ is focused on the physicality of oppression and marginality, typically based on race, ethnicity, socioeconomic status, gender, sexual orientation, age, disability, physical appearance and illness; and (3) the ‘client body,’ which reflects the bodily experiences of ‘clients’ who are ‘marked, scarred, transformed, and written upon or constructed by the various regimes of institutional, discursive, and non-discursive power.’<sup>168,169</sup> The multiple dimensions of the ‘body’ account for women’s social construction of their identities and their resultant perceived physical and mental HRQoL.

## Chapter 5

### **Personal reflections regarding power dynamics between researcher and participant and integrating quantitative and qualitative methodologies in the production of knowledge**

The purpose of this mixed methods study was to build knowledge regarding the relationship between HIV/ HSV-2 co-infections and HRQoL. I had concern about how the stories and experiences of HIV-positive women would be represented in the production of knowledge about HIV and HSV-2 co-infection and wanted to ensure that the practice of reciprocity was incorporated into both the quantitative and qualitative phases. Maiter compares reciprocity to the respectful nature of good research relationships where reciprocal dialogue exchanges occur and the individual researcher and study participant communicate and converse as equals.<sup>173</sup> This dialogue between researcher and participant emphasizes the avoidance of harm while encouraging the establishment of a working relationship that can be beneficial to all parties involved. Whether participants were being asked to complete a self-report questionnaire or engage in a dialogue about their personal experience, I viewed my relationship with them as an equitable partnership. I was transparent regarding the purpose of the research and what they could expect by participating and having the opportunity to share their story. Maiter highlights the fact that medical sciences have not been attentive to social relationships that may occur ‘inside’ the research process; instead, health research has embraced the ‘expert’ perspective, adopting an objectivist and value-free stance that discourages reflection regarding interdependencies among researchers and participants.<sup>173</sup> The purpose of this mixed methods study was to not take on the role as an ‘expert,’ rather it was to socially engage with the women to understand their stories. Riessman highlights the danger of adopting an objectivist and value-free stance when conducting research,

pointing out that although interviewing is a scientific method of data collection and analysis, it is a social practice and human enterprise, and not the work of robots programmed to collect pure information.<sup>174</sup> Riessman further states that researchers should be aware of tensions they may experience during an interview where their allegiance to ‘scientific’ interviewing practice with its norms of distance and objectivity conflicts with a possible allegiance to women’s culture with its norms of empathy and subjectivity.<sup>174</sup> Research is not value-free nor is it completely objective. It was impossible to conduct research on a topic of a sensitive nature such as HIV/AIDS and genital herpes without exhibiting empathy and subjectivity, and without considering the relationships that may have been established between myself as the researcher and the participants. As a researcher, I was asking women to complete surveys and answer questions during in-person interviews that explored topics of a very personal nature; these women were willing to participate and share their experiences living with HIV and HSV-2 co-infections. It was my ethical responsibility as a researcher to ensure that the space in which they shared their story was safe, private and confidential and that the women felt comfortable to participate in an equitable dialogue before the qualitative interview began. Throughout the interview, I needed to be constantly aware and ready for cues as to how these women may have felt engaging in a discussion about personal topics.

It was also important to consider the emotions that women may have experienced recounting their realities of living with HIV and genital herpes. During the informed consent process, the risk of discomfort and emotional disturbance was discussed. Participants were aware of the nature of questions that would be asked of them. Participants were also encouraged to seek social or emotional support from a trusted

friend or service provider following the interview if they experienced discomfort. These actions were in line with Hubbard's recommendation that qualitative researchers must acknowledge the emotional domain in research, and take into account the emotional risk for respondents.<sup>175</sup> As Maiter describes, the connection between researcher and participant intensifies over the course of the interview; researchers need to be conscientious and try to discern what it is participants are seeking.<sup>173</sup> Some of these women had experienced HIV-related stigma, discrimination and other forms of oppression and marginalization. Central to the concept of reciprocity, I had to level the 'playing field' and address power dynamics explicitly; it was imperative that I did not engage in research practices that would further marginalize the participants or make them feel objectified.<sup>173</sup> I ran the risk of categorizing women into 'typologies,' which would have gone against the tenets of interpretive phenomenology of exploring and understanding the unique meaning and experiences of participants. Stamm et al. claimed to use qualitative research methods in their exploration of individuals' experiences with rheumatoid arthritis, namely, the narrative biographic method, which "combines narrative understanding and contextuality in order to explore the unique textual and naturalistic experiences of a single individual from the perspective of the told life story."<sup>176</sup> Instead, Stamm et al. conducted a superficial analysis of narratives creating two 'typologies' of how life with rheumatoid arthritis was managed from the multiple life stories of participants. Stamm et al. contradicted their methodology of exploring the "unique textual and naturalistic experiences of a single individual" by stating that a typology could not emerge out of the analysis of only one life story.<sup>176</sup> By fitting the participants' experiences of rheumatoid arthritis into limited 'typologies,' Stamm et al. lost the

uniqueness of each participant's narrative; the participant narratives were not portrayed in an ethical manner and, in the end, their individual voices were not heard.

The process of representing and reporting individual narratives relates to the language that participants use throughout an interview as well as the language that is used by researchers in knowledge translation and exchange activities. Sinding explores the concept of portrayal stating, "in writing and speaking about research participants, researchers make countless choices...We decide what is important about their stories and we say what their stories 'really mean'...marginalized groups have often not fared well."<sup>177</sup> Sinding continues echoing Shope: "The extent to which research participants recognize their lives in researchers' words is questionable."<sup>177,178</sup> This observation is worrisome and relates to a disconnection between what is 'said' by participants during an interview and what may be 'heard' by the researcher. Poindexter<sup>179</sup> and Riessman<sup>174</sup> further relate the ambiguity in research interviewing to the degree of insider knowledge that the researcher holds in relation to the participant group, especially considering narration of personal experience can take many forms. Investigators may miss or misinterpret the participants' words due to style of narration, which is influenced by class, age, religious background, regional origin, ethnicity and sexual orientation; or become confused and not 'hear' what is important to the narrator because of linguistic, experiential, theoretical, and cultural filters or disparate frames of reference.<sup>174,179</sup> This lack of having footing or history in their worlds as well as a lack of shared cultural norms for telling a story or giving an explanation can create barriers to understanding.<sup>174</sup> As a novice qualitative researcher, I had to be cognizant of the demographic and cultural differences between the women who participated in this study and myself as researcher,

and not ignore these social realities, but attempt to understand how these differences may have affected data collection and analysis. I also needed to consider what I may have had in common with the participants and how this may have influenced the interviews.

Boushel reconceptualizes this partial overlap of experience and perspective that may link researcher and researched as an ‘experiential affinity’ rather than an ‘insider’ perspective; this ‘experiential affinity’ is fluid and dynamic, and can change depending on a researcher’s social, historical and cultural context compared to that of the participants.<sup>180</sup>

LaSala argues that good research incorporates an integration of insider knowledge, or ‘experiential affinity,’ and outsider knowledge, renamed as emic and etic perspectives, respectively.<sup>181</sup> The emic perspective is the viewpoint of the members of the group or culture being studied; behaviour and events are described strictly in terms of what they mean to the informants.<sup>181</sup> From the etic perspective, behaviour is explained using theories that are thought to be applicable to all groups and cultures.<sup>181</sup> In order to ensure that I ‘heard’ what each participant was telling me, I framed, displayed and reported their narratives in their own words; and strove to ensure that the development of their life histories during the interview was a collaborative and interactive process.<sup>174</sup> I also considered the degree to which I possessed an emic perspective or an ‘experiential affinity’ with the women who participated in the interviews, as well as how I may have been positioned from the etic, or outsider, perspective. Although I have studied, worked and volunteered in the field of HIV/AIDS for over 8 years and possess a degree of emic perspective of the HIV culture and community as an ally, I am not a person living with HIV and HSV-2 infections, therefore, lack important ‘insider’ knowledge. There were ways that I related to the women, for example, as another woman, because of my own

personal experiences with taboo subjects of sex, sexuality and sexually transmitted infections, as well as through congruent geographic, cultural and generational contexts, which produced an unspoken but shared assumptive world.<sup>174</sup> Perfect congruity was not, and is rarely possible;<sup>174</sup> researchers will always be outsiders in some way, and we need to be honest and transparent about that reality.<sup>179</sup>

I also struggled with the power and privilege that I possessed as a researcher with access to personal information that was collected from women during the quantitative data collection; and how knowing this information may have affected the qualitative phase of the study. The information that I am privileged to as a researcher emphasizes the vulnerabilities of these women, who took the time to answer survey questions exploring intimate details of their sexuality and sexual health. For example, the study survey asked questions about their history of sexually transmitted infections, previous sexual encounters, pregnancy and reproductive health history, how the women acquired HIV, as well as about markers of socioeconomic status including household income and educational level attained. This information was incorporated into the statistical analysis, and I was aware of this information prior to meeting with women for their in-depth interview. I was challenged with how this sensitive information may have stimulated an emotional response, and how these emotions may have affected the qualitative data collection, interpretation and participant-researcher engagement and dialogue. Hubbard has acknowledged that researchers are not immune to emotional experiences in the field and must pay attention to the ‘emotional dangers’ inherent in qualitative research.<sup>175</sup> After reading Hubbard’s article and considering the different research projects I have been involved with, I came to the conclusion that doing qualitative research, but also



quantitative research, is a natural process of self-reflexivity taking the researcher on an emotional and personal journey. The knowledge acquired by engaging in research is not objective nor removed from our own bodies, but is created through our experiences of the world and has epistemological significance.<sup>175</sup> These emotions that researchers experience encompass important cognitive and analytic resources, which are capable of yielding significant sociological insights. As Hubbard points out, the emotional response that is experienced doing research can enrich one's understanding of what is meaningful to those being interviewed or engaged in quantitative research, bringing the researcher closer to the participants' local knowledge and truth.<sup>175</sup> In light of the role of emotions in the research process, Hubbard suggests having strategies in place prior to starting qualitative, in-depth interviews in order to reduce participant distress and provide a degree of protection for both the participant and the researcher.<sup>175</sup> Strategies used in this study included anticipating problems or issues that may have arisen and evoked emotion, debriefing with colleagues and mentors after interviews, offering rest breaks during the interview and pacing the interview so that topics emerged gradually. I also needed to acknowledge and consider how the emotionality of one interview setting may have influenced how I managed emotion in the next.<sup>175</sup> More broadly, I continually reflected and considered how the emotions that I experienced affected quantitative and qualitative data collection, analysis and interpretation.

Health challenges in the context of HIV infection have predominantly been explored using quantitative research methods situated within a positivist methodological paradigm whereby research questions are developed by clinicians and academic

researchers and conclusions are drawn from the statistical analyses of data collected in randomized controlled trials and/or observational cohort studies.

I had concern regarding how to effectively integrate quantitative and qualitative research methods into one mixed methods study as these methods are situated in different and often conflicting theoretical and methodological paradigms. As Neuman points out, a positivist theoretical and methodological paradigm enables the organized combination of deductive logic and precise empirical observations of individual behaviour in order to confirm a set of probabilistic causal laws to predict general patterns of human activity.<sup>184</sup> Positivism relies heavily on the notions of generalizability, reliability through reproducibility and logical reasoning; and the conduct of research is value-free and objective. These concepts aligned with the study objectives and methods that were agreed to by the clinician and basic scientist research team when the HSV/HIV co-infection study began in 2005.

Interpretive social science is a theoretical and methodological perspective that was incorporated in the exploration and description of women's narratives. Citing Neuman, interpretive methodologies are a traditional form of qualitative research emphasizing an in-depth and inductive examination of text in order to learn what is meaningful and relevant to the people being studied, as well as how they experience everyday life holding the belief that social life is based on social interactions and socially constructed meaning systems.<sup>184</sup> In developing this thesis project, it was decided to align conclusions drawn during the qualitative phase with the general tenets of naturalistic inquiry; emerging themes and concepts were grounded in the data rather than deducing testable hypotheses from existing theories.<sup>143</sup> Emerging themes and concepts also focused

on the meaning and narratives of the study participants who experienced the phenomenon of interest without imposing a priori conceptualizations or prepositions.<sup>139,143,144</sup>

In attempting to rationalize how and why positivist and interpretive theoretical and methodological approaches could be integrated into one study, I thought more broadly about why this new knowledge about living with HIV and HSV-2 co-infections was being created and for whose benefit. Originally, the study was designed to fill a knowledge void regarding the biological synergy between HIV and Herpesviruses. It was appropriate to employ positivist, quantitative research methods in order to understand biological and statistical relationships. The new knowledge produced from the quantitative phase regarding sero-prevalence of Herpesviruses in HIV-positive women and statistical associations between co-infection and HRQoL would potentially benefit clinicians to provide improved, evidence-based care to HIV-positive women. HIV-positive women would also potentially benefit from this new knowledge as recipients of this improved, evidence-based care. By positioning the qualitative phase within an interpretive phenomenological theoretical and methodological paradigm, women's narratives were showcased and their local knowledge was contextualized within broader social, cultural and political systems. The new knowledge produced from the qualitative phase regarding women's experiences living with HIV and HSV-2 co-infections would potentially benefit other HIV-positive women in advocating for improved health care services and delivery, expansion of funding for research and care in co-infections, co-morbidities and other social determinants of health, as well as expanding education and support programming for women regarding co-infections and co-morbidities. The construction of knowledge in the field of HIV/HSV-2 co-infection can be attentive to

both positivist and interpretive research goals. Both outcomes of interest, including the investigation of biological, clinical and statistical relationships and understanding how HIV-positive women experience daily life within broader socially constructed meaning systems, was achievable.

In order to stay in line with the theoretical underpinnings of both positivist quantitative research and interpretive qualitative research, it was decided to operate within a transformative paradigm, which enables the combination of quantitative and qualitative methods while addressing inequality and injustice in society.<sup>185</sup> Mertens describes a transformative paradigm as one that recognizes the construction of realities with influence from the social, political, cultural, economic and racial values in one's world; with power and privilege determining whose reality and knowledge is privileged in a research context.<sup>185</sup> In reviewing the general tenets of the transformative paradigm, I found that my own theoretical perspective as a researcher and the methods employed throughout this thesis aligned with this paradigm epistemologically and methodologically.

The epistemological stance of the transformative paradigm is concerned with the relationship between the person who 'knows' with the would-be-known; to know realities it is paramount to have an interactive and trusting link between the researcher and the participants.<sup>185</sup> Throughout the progression of the HSV/HIV co-infection study, my relationship with the participants developed to a point where I was comfortable asking them to share their story living with HIV and HSV-2 co-infections and they were comfortable accepting the invitation. In the development of this thesis, conversational and interactive qualitative interviews were deliberately selected as a research

methodology in order to create a space where women could share their stories and I could bear witness to their experiences as a researcher.

The methodological stance of the transformative paradigm is concerned with power; power issues should be explicitly addressed and issues of discrimination and oppression should be recognized in the researcher-participant dynamic.<sup>185</sup> As part of the informed consent process for both the quantitative and qualitative phases and through informal conversations with the women, I was transparent about my positioning as a graduate student researcher and had a dialogue with them about the purpose of the research as well as how and why the data collected would be used.

It was not possible to capture all elements of the transformative paradigm in this study. The transformative paradigm places a great deal of importance on involving community members in the initial discussions of the research focus as an important way to gather insight.<sup>185</sup> This was not logistically possible for the HSV/HIV co-infection study; there was no community involvement in the development of both the quantitative and qualitative research questions and methods other than through informal conversations with the women already enrolled in the quantitative phase of the study when they were attending clinic appointments. Another central tenet of the transformative paradigm is that power must be addressed at each stage of the research process.<sup>185</sup> It was only possible to observe and reflect how power dynamics may have influenced the data collection and analysis in the qualitative phase. Speculation was the only way to consider power dynamics in the quantitative data collection since this phase was nearing completion when the decision was made to investigate HSV/HIV co-infection for this thesis. Regardless, it was possible to incorporate a theoretical and methodological

paradigm that aligned with my beliefs as a researcher, while enabling the integration of positivist, quantitative and interpretive, qualitative research methods. As Mertens points out, the transformative paradigm qualitative dimension highlights the need and value of the community's perspective and voice, while the quantitative dimension provides the opportunity to demonstrate outcomes that have credibility for both the HIV-positive women's community as well as academic scholars.<sup>185</sup>

This mixed methods research study contributed to the body of knowledge regarding how HSV/HIV co-infection affects women's perceived physical and mental HRQoL. Chilisa recommends that the point of reference for legitimating research findings should be on the basis of an accumulated body of knowledge that is created by the people affected by the phenomenon.<sup>186</sup> In agreement with this line of thinking, but also wanting to triangulate and integrate qualitative and quantitative findings, I stayed intimately linked to HIV-positive women's narratives. I ensured that their voices, which were important and legitimate contributions to driving the HIV/HSV co-infection research agenda forward, were heard loudly and clearly.

**Appendix A – Sample size calculations**

**How many people per group would be needed to detect a small, moderate or large difference in HRQoL?**

As per Norman and Streiner:  $n = 2 \left[ \frac{\{(Z_\alpha + Z_\beta) \sigma\}}{\Delta} \right]^2$   
 $Z_\alpha = -1.96$  (based on  $\alpha=0.025$ );  $Z_\beta = -0.84$  (based on  $\beta=0.20$ );  $\sigma = 10$  (of MOS-HIV and SF-12v2)

<p><b>2-point or small difference:</b>  <math>\Delta=2</math>  <math>n = 2 \left[ \frac{\{(Z_\alpha + Z_\beta) \sigma\}}{\Delta} \right]^2</math>  <math>n = 2 \left[ \frac{\{(-1.96 - 0.84)10\}}{2} \right]^2</math>  <math>n = 2 \left[ \frac{-28}{2} \right]^2</math>  <math>n = 392</math> (per group)</p>	<p><b>5-point or moderate difference:</b>  <math>\Delta=5</math>  <math>n = 2 \left[ \frac{\{(Z_\alpha + Z_\beta) \sigma\}}{\Delta} \right]^2</math>  <math>n = 2 \left[ \frac{\{(-1.96 - 0.84)10\}}{5} \right]^2</math>  <math>n = 2 \left[ \frac{-28}{5} \right]^2</math>  <math>n = 62.7</math> or 63 per group</p>	<p><b>8-point or large difference:</b>  <math>\Delta=8</math>  <math>n = 2 \left[ \frac{\{(Z_\alpha + Z_\beta) \sigma\}}{\Delta} \right]^2</math>  <math>n = 2 \left[ \frac{\{(-1.96 - 0.84)10\}}{8} \right]^2</math>  <math>n = 2 \left[ \frac{-28}{8} \right]^2</math>  <math>n = 24.5</math> or 25 per group</p>
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**How much power did the study have with its resultant sample size to detect a difference between groups?**

As per Norman and Streiner, because the two groups differ in number, use the harmonic mean for the sample size (n):

$HM = 2 / \left[ \frac{1}{25} + \frac{1}{64} \right] = 2 / \left[ \frac{89}{1600} \right] = 40.4$  per group

Using Table E in Norman and Streiner (page 363) and assuming  $\alpha=0.05$  (two-tailed):

<p><b>2-point or small difference:</b>  <math>d = 2/10 = 0.2</math>                  Power = 0.143 or 14%</p>	<p><b>5-point or moderate difference:</b>  <math>d = 5/10 = 0.5</math>  <math>d = 0.4 \rightarrow</math> power = 0.442  <math>d = 0.6 \rightarrow</math> power = 0.773                  Power at <math>d=0.05</math>:                  Power = <math>(0.442+0.773)/2</math>                  Power = 0.6075 or 61%</p>	<p><b>8-point or large difference:</b>  <math>d = 8/10 = 0.8</math>                  Power = 0.949 or 95%</p>
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**Table 1 – Descriptive statistics of the cohort (n=89)**

<b>Variable</b>	<b>Mean (SD); Min-Max</b>
Age	42.2 (9.4); 21-67
Nadir CD4 cell count	271 (169); 2-838
Current CD4 cell count	519 (259); 100-1200
Current Log Viral Load (log copies/ml blood)	2.5 (1.1); 1.7-5.1
Number of years living with HIV	8 (4.8); 1-23
MOS-HIV Physical Health Summary Score	50.8 (11.4); 17.9-66.6
MOS-HIV Mental Health Summary Score	49.0 (11.1); 16.5-67.4
SF-12v2 Physical Health Summary Score	49.9 (10.4); 19.3-68.2
SF-12v2 Mental Health Summary Score	45.3 (10.1); 17.0-66.1
	<b>N (%)</b>
HSV-2 positive	64 (71.9)
HSV-1 positive	53 (59.6)
CMV Antibody positive	70 (78.7) – n=85
Presence of Anxiety	51 (57.3) – n=88
Presence of Depression	11 (12.4) – n=88
On HAART at study enrolment	64 (71.9)
Number of women virally suppressed (i.e. HIV viral load less than 50 copies/ml)	51 (57.3)
Currently or ever received treatment for HSV	12 (13.5)
Ethnicity	
<i>Caucasian</i>	38 (42.7)
<i>Black</i>	41 (46.1)
<i>First Nation</i>	3 (3.4)
<i>South Asian</i>	2 (2.2)
<i>Other</i>	3 (3.4)
Place of Origin	
<i>Canadian Born</i>	37 (41.6)
<i>African Born</i>	37 (41.6)
<i>Other</i>	15 (16.8)
HIV Risk Factor	
<i>Heterosexual partner</i>	73 (82)
<i>Injection Drug Use</i>	3 (3.4)
<i>Blood Transfusion or Blood Products</i>	3 (3.4)
<i>Unknown</i>	10 (11.2)
Completed Education	
<i>Secondary school education</i>	38 (42.7)
<i>College or trade school education</i>	39 (43.8)
<i>University</i>	12 (13.5)
Primary Source of Income	
<i>Social or Government Assistance</i>	43 (48.3)
<i>Wages/Salaries of Employment</i>	37 (41.6)
<i>Self-Employment</i>	5 (5.6)
<i>Worker's Compensation</i>	2 (2.2)
<i>Pension</i>	2 (2.2)
Total Income Per Year	
<i>\$0-14,999</i>	36 (40.4)
<i>\$15-19,999</i>	14 (15.7)
<i>\$20-29,999</i>	11 (12.4)
<i>\$30-39,999</i>	8 (9.0)
<i>\$40-49,999</i>	4 (4.5)
<i>&gt;\$50,000</i>	13 (14.6)
<i>Unknown</i>	3 (3.3)



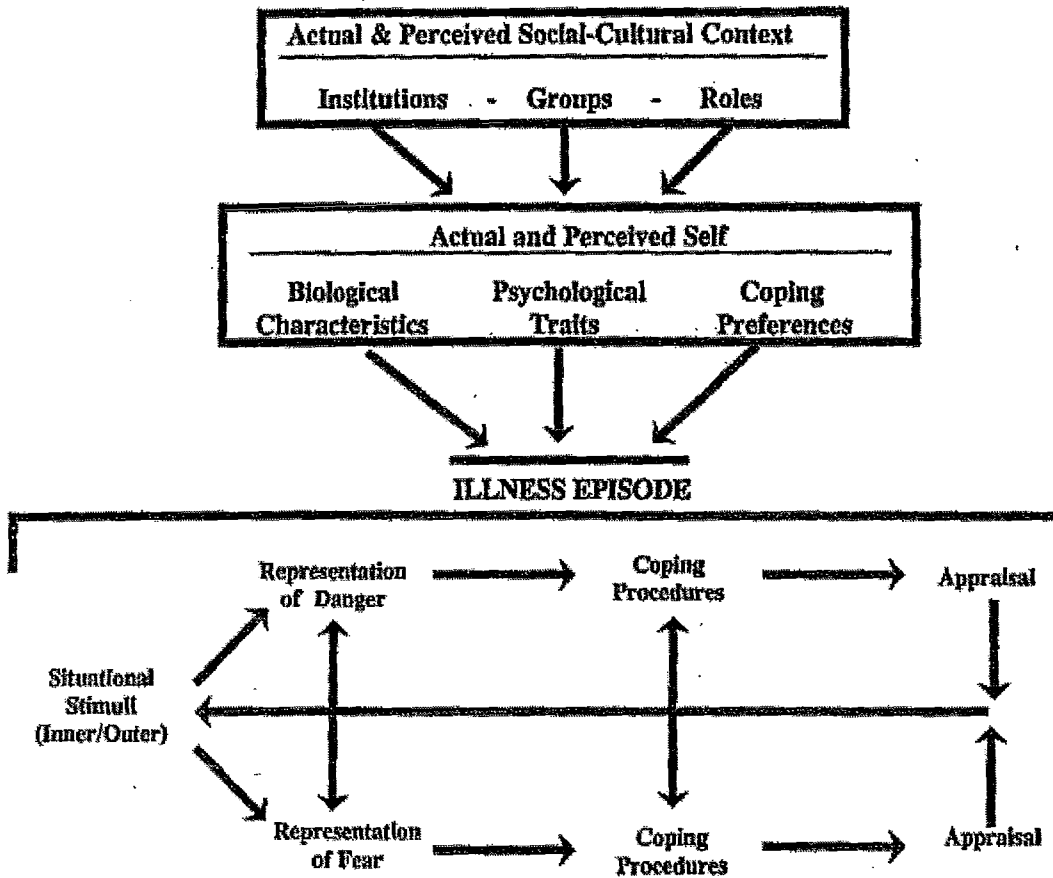
**Table 2 – Differences between HSV-2/HIV co-infected women and women infected with HIV alone**

Variable	HSV-2 positive (n=64) Mean (SD)	HSV-2 negative (n=25) Mean (SD)	Independent Samples T Test	Mean Difference (95% CI)
MOS-HIV PHS	52.5 (10.3)	46.6 (13.1)	p=0.027	-5.91 (-11.13, -6.89)
MOS-HIV MHS	51.0 (10.7)	44.0 (10.8)	p=0.007	-7.01 (-12.05, -1.98)
SF-12v2 PHS	49.8 (9.6)	50.0 (12.6)	p=0.924	0.24 (-4.69, 5.16)
SF-12v2 MHS	45.8 (8.4)	43.7 (13.6)	p=0.471	-2.13 (-8.08, 3.82)
Age	42.7 (9.6)	40.8 (9.1)	p=0.401	-1.88 (-6.31, 2.55)
Current CD4 cell count	538 (253)	471 (274)	p=0.282	-66.18 (-187.56, 55.20)
Years living with HIV	7.9 (5.1)	8.4 (4.2)	p=0.663	0.50 (-1.77, 2.78)
	<b>N (%)</b>	<b>N (%)</b>	<b>Odds Ratio</b>	<b>95% CI</b>
Anxiety	37 (59)	14 (56)	1.12	0.44-2.85
Depression	6 (10)	5 (20)	0.42	0.12-1.53
History of genital herpes symptoms	14 (22)	3 (12)	2.05	0.54-7.87
History of drug use (including cocaine, opiates, marijuana)	10 (16)	3 (12)	1.36	0.34-5.41
Canadian Born	23 (36)	14 (56)	0.44	0.17-1.13
African Born	31 (48)	6 (24)	2.98	1.05-8.42

**Table 3 – Multivariable linear regression**

<b>Variable</b>	<b>MOS-HIV PHS</b>	<b>SF-12v2 PHS</b>	<b>MOS-HIV MHS</b>	<b>SF-12v2 MHS</b>
Adjusted R <sup>2</sup>	0.137	0.062	0.083	0.011
F test, p value	3.798, p=0.004	2.155, p=0.067	2.599, p=0.031	0.802, p=0.552
	<b>β, p value</b>	<b>β, p value</b>	<b>β, p value</b>	<b>B, p value</b>
HSV-2 positive	5.27, p=0.046	-1.45, p=0.561	6.63, p=0.013	2.24, p=0.372
Age per 10 years	-2.52, p=0.040	-1.87, p=0.109	-0.29, p=0.812	0.63, p=0.586
Current CD4 cell count	-0.004, p=0.354	0.004, p=0.309	-0.002, p=0.690	-0.006, p=0.157
Current receipt of HAART	2.34, p=0.364	1.19, p=0.627	4.90, p=0.061	2.53, p=0.306
African-born	5.70, p=0.018	5.22, p=0.024	2.31, p=0.336	0.74, p=0.745

Figure 1 – Leventhal, Leventhal and Cameron's self-regulation of illness model



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