

Cardiovascular Disease Risk Behaviors in  
Human Immunodeficiency Virus-Positive Populations:  
Exploring a Stress-Coping Hypothesis

Anton Palma

Submitted in partial fulfillment of the  
requirements for the degree of  
Doctor of Philosophy  
under the Executive Committee  
of the Graduate School of Arts and Sciences

COLUMBIA UNIVERSITY

2020

© 2019  
Anton Palma  
All rights reserved

## **ABSTRACT**

### **Cardiovascular Disease Risk Behaviors in Human Immunodeficiency Virus-Positive Populations: Exploring a Stress-Coping Hypothesis**

Anton Palma

Cardiovascular disease (CVD) risk behaviors, namely tobacco smoking, hazardous alcohol use, poor diet and sedentary behavior, are more prevalent among people living with HIV (PLWH) than the general population. Qualitative evidence shows that PLWH report adopting unhealthy behaviors as a means of coping with the stress of living with HIV, including the adverse physiological symptoms of HIV infection, the psychological stress of being aware of one's HIV status, and the physiological and psychological impacts of being on HIV treatment. These observations suggest that being HIV-positive may have a causal influence on CVD risk behaviors and that these causal effects likely differ across stages of the HIV continuum. To date, few quantitative studies have been conducted to examine these causal relationships. The goal of this dissertation was to explore the effects of HIV continuum stage on CVD risk behaviors and assess several plausible stress-coping mechanisms, as motivated by established stress-coping theory. This dissertation consisted of three studies. First, a systematic review was conducted to examine the existing quantitative evidence for the causal effects of HIV continuum stage on CVD risk behaviors. Findings from this review revealed that being HIV-positive is associated with excess smoking and drinking, and that while receipt of a positive HIV diagnosis is associated with short-term improvements in some CVD risk behaviors, these improvements are unlikely to be maintained long-term. Overall, however, the existing studies suffer important methodological limitations, notably inadequate characterization of HIV continuum stage. The second study was an empirical analysis of patterns of self-reported CVD risk behaviors across

the HIV continuum among a population-based sample of 4,061 adults aged 40 years and over living in rural Agincourt district in South Africa. Results showed no consistent evidence of an association between HIV continuum stage and hazardous alcohol use or sedentary behavior. However, higher prevalence of smoking was observed specifically among males who were HIV-positive and aware of their status but not on treatment, compared to those who were HIV-negative. There was no evidence of mediation by various measures of physiological and/or psychological stress. The third study was an analysis of whether perceived life expectancy (PLE) modifies the effects of HIV continuum stage on CVD risk behaviors. Observed associations were most prominent among individuals with low PLE and null among those with high PLE. Overall, this dissertation contributed to greater understanding of the relationship between CVD risk behaviors among HIV-infected persons across the HIV continuum. Findings did not support a stress-coping hypothesis; however, PLE was found to be a potentially useful indicator of individuals who are most likely to smoke in the presence of HIV. This dissertation also fills evidence gaps among older adults in sub-Saharan Africa, an under-studied population with high and increasing burdens of both HIV and CVD. As HIV-positive population survive longer on antiretroviral therapy and the prevention of age-related conditions becomes increasingly important, these findings may help inform future research and the development of CVD prevention interventions.

## TABLE OF CONTENTS

<b>LIST OF FIGURES AND TABLES.....</b>	<b>iv</b>
<b>ACKNOWLEDGEMENTS .....</b>	<b>vi</b>
<b>DEDICATION.....</b>	<b>viii</b>
<b>CHAPTER 1.INTRODUCTION.....</b>	<b>1</b>
1.1. Background.....	1
1.1.1. <i>Cardiovascular disease risk behaviors in HIV</i> .....	1
1.1.2. <i>Does HIV itself influence CVD risk behaviors?</i> .....	2
1.2. Stress-coping theory.....	3
1.3. Dissertation overview .....	5
1.4. References.....	6
<b>CHAPTER 2.DOES HIV CAUSE CARDIOVASCULAR DISEASE RISK BEHAVIORS?     A SYSTEMATIC REVIEW OF EVIDENCE ACROSS THE HIV CONTINUUM</b>	<b>13</b>
2.1. Abstract.....	13
2.1. Introduction.....	15
2.2. Methods.....	17
2.3. Results.....	19
2.3.1. <i>Smoking</i> .....	20
2.3.2. <i>Alcohol use</i> .....	22
2.3.3. <i>Dietary behavior</i> .....	23
2.3.4. <i>Sedentary behavior</i> .....	23
2.4. Discussion.....	24
2.4.1. <i>Strengths and limitations</i> .....	27
2.5. Conclusion .....	28
2.6. References.....	29
2.7. Figures and Tables .....	40
<b>CHAPTER 3.PATTERNS OF CARDIOVASCULAR DISEASE RISK BEHAVIORS     ACROSS THE HIV CONTINUUM: DATA FROM A POPULATION-BASED     STUDY OF OLDER ADULTS IN RURAL SOUTH AFRICA.....</b>	<b>48</b>

3.1. Abstract.....	48
3.2. Introduction.....	50
3.3. Methods.....	53
3.3.1. <i>Data source</i> .....	53
3.3.2. <i>Measures</i> .....	54
3.3.3. <i>Analysis</i> .....	57
3.3.4. <i>Sensitivity analyses</i> .....	58
3.4. Results.....	59
3.4.1. <i>Participant characteristics</i> .....	59
3.4.2. <i>CVD risk behavior patterns</i> .....	60
3.4.3. <i>Mediation analyses</i> .....	61
3.4.4. <i>Sensitivity analyses</i> .....	62
3.5. Discussion.....	63
3.5.1. <i>Limitations</i> .....	66
3.6. Conclusion .....	68
3.7. References.....	70
3.8. Figures and Tables .....	78

**CHAPTER 4. DOES PERCEIVED LIFE EXPECTANCY MODIFY THE EFFECTS OF HIV ON CVD RISK BEHAVIORS? A SELF-REGULATION HYPOTHESIS ..... 89**

4.1. Abstract.....	89
4.2. Introduction.....	91
4.3. Methods.....	94
4.3.1. <i>Data source</i> .....	94
4.3.2. <i>Measures</i> .....	95
4.3.3. <i>Analysis</i> .....	96
4.3.4. <i>Sensitivity analyses</i> .....	97
4.4. Results.....	99
4.4.1. <i>Sample characteristics</i> .....	99
4.4.2. <i>Regression models</i> .....	100

4.4.3. <i>Sensitivity analyses</i> .....	101
4.5. Discussion.....	102
4.6. Conclusion .....	106
4.7. References.....	107
4.8. Figures and Tables .....	113
<b>CHAPTER 5. CONCLUSION .....</b>	<b>127</b>
5.1. Overview.....	127
5.2. Summary.....	127
5.3. Strengths and limitations.....	129
5.4. Implications for public health and future research .....	131
<b>APPENDICES.....</b>	<b>133</b>

## LIST OF FIGURES AND TABLES

Figure 2.1 Systematic review flowchart .....	40
Table 2.1 Longitudinal analyses of smoking change by HIV continuum stage .....	41
Table 2.2 Longitudinal analyses of alcohol use change by HIV continuum stage .....	43
Table 2.3 Longitudinal analyses of dietary behavior change by HIV continuum stage .....	45
Table 2.4 Longitudinal analyses of sedentary behavior change by HIV continuum stage .....	45
Table 2.5 Summary of study characteristics for all CVD risk behaviors .....	46
Table 2.6 Summary of findings of longitudinal studies for all CVD risk behaviors .....	47
Figure 3.1 Conceptual diagram of causal pathways between HIV continuum stage and CVD risk behaviors mediated by physiological and psychological symptoms .....	78
Figure 3.2 Sample eligibility flowchart .....	79
Table 3.1 Sample characteristics, adults aged 40 years and older residing in rural Agincourt district, South Africa, enrolled in HAALSI study, 2014-2015 (n=4,061) .....	80
Table 3.2 Prevalence ratios (PRs) for CVD risk behavior by HIV continuum stage, overall and by sex .....	81
Figure 3.3 Predicted prevalence <sup>1</sup> of 3 CVD risk behaviors by HIV continuum stage .....	82
Figure 3.4 Predicted prevalence <sup>1</sup> of 3 CVD risk behaviors by HIV continuum stage and sex ....	83
Table 3.3 Prevalence (95% CI) of hypothesized mediators by HIV continuum stage and by outcome .....	84
Table 3.4 Adjusted prevalence ratios (PRs) for CVD risk behavior by HIV continuum stage, controlling for individual mediators .....	85
Figure 3.5 Forest plot of prevalence ratios for CVD risk behaviors by HIV continuum stage, controlling for mediators .....	86
Table 3.5 Comparison of complete case analysis and MI regression model results .....	87
Table 3.6 Sensitivity analyses for alternate exposure definitions .....	88
Figure 4.1 Conceptual diagram of relationship between HIV continuum stage, low perceived life expectancy (PLE) and CVD risk behaviors .....	113
Figure 4.2 Illustration of model for perceived life expectancy (PLE) and extraction of PLE trait component, $\epsilon_i$ .....	113
Figure 4.3 Sample eligibility flowchart for effect modification analysis .....	114
Table 4.1 Sample characteristics .....	115
Figure 4.4 Distribution of perceived life expectancy .....	116
Table 4.2 Prevalence ratios (PRs) for 3 CVD risk behaviors across joint categories of HIV continuum stage and perceived life expectancy (PLE) (n=3,232) .....	117
Figure 4.5 Predicted prevalence of 3 CVD risk behaviors by HIV continuum stage and PLE ..	118
Table 4.3 Regression model to extracting PLE trait component (residuals) .....	119
Figure 4.6 Distribution of residuals of perceived life expectancy (PLE) .....	120
Table 4.5. Concordance between low perceived life expectancy (PLE) as measured and trait component .....	120
Table 4.6 Sensitivity analyses for alternative PLE definitions: tobacco smoking .....	121
Table 4.7 Sensitivity analyses for alternative PLE definitions: hazardous alcohol use .....	122
Table 4.8 Sensitivity analyses for alternative PLE definitions: sedentary behavior .....	123
Figure 4.7 Sensitivity analyses, predicted prevalence of smoking .....	124
Figure 4.8 Sensitivity analyses, predicted prevalence of hazardous alcohol use .....	125
Figure 4.9 Sensitivity analyses, predicted prevalence of sedentary behavior .....	126
Appendix Table 5.1 Search terms used in systematic literature review .....	133

Appendix Table 5.2 Cross-sectional analyses of smoking by HIV continuum stage.....	134
Appendix Table 5.3 Cross-sectional analyses of alcohol use by HIV continuum stage.....	139
Appendix Table 5.4 Cross-sectional analyses of dietary behavior by HIV continuum stage.....	147
Appendix Table 5.5 Cross-sectional analyses of sedentary behavior by HIV continuum stage	147
Appendix Table 5.6 Summary of systematic review findings .....	148
Appendix Table 5.7 AUDIT-C questionnaire for hazardous alcohol use.....	149
Appendix Table 5.8 IPAQ scoring for physical activity.....	150
Appendix Table 5.9 Measures of physiological and psychological HIV-related stress .....	152
Appendix Table 5.10 Bivariate associations between hypothesized confounders and exposure and outcome variables.....	154
Appendix Table 5.11 Predicted prevalence of CVD risk behaviors by HIV continuum stage overall, and stratified by sex .....	155
Appendix Table 5.12 Comparison of complete case sample and multiple imputation (MI) sample .....	156
Appendix Table 5.13 Comparison of complete case sample and full baseline cohort .....	157

## ACKNOWLEDGEMENTS

This dissertation would not have been possible without the support of numerous people. I would like to thank my dissertation committee for their immeasurable generosity and thoughtful contributions to this work. I am especially indebted to my dissertation sponsor, Dr. Matthew Lamb, who has been my most trusted mentor. His patient coaching sharpened my thinking and reasoning skills, and his pragmatism gave me the confidence to always keep forging ahead. My dissertation chair, Dr. Wafaa El-Sadr, has always been an inspiration and gracious advocate for me at many points during the program. I will always be grateful for Wafaa's generous time and effort in helping me brainstorm ideas at my times of greatest need during the program and for opening my mind and improve my writing. I would also like to thank Dr. Susie Hoffman for her careful reading of many iterations of my dissertation and for challenging me to think more critically about my work, giving it depth I could not have accomplished on my own. A warm thank you to Dr. Andrea Norcini Pala for providing invaluable substantive expertise and practical advice as I developed the topic. Last but not least, sincerest thanks to Dr. Till Barnighausen whose research laid the foundation I built upon for this dissertation and whose enthusiasm is a constant source of motivation and energy.

I would like to acknowledge the HAALSI study team at the Harvard School of Public Health, especially Julia Rohr and Livia Montana for connecting me with and providing guidance about the data. Thank you to the Global HIV Implementation Science Training Fellowship for providing funding and training support during my doctoral program. Special thanks to Dr. Miriam Rabkin for her mentorship and for cultivating my interests in global HIV/NCD health. Thanks also to Dr. Stephen Arpadi who would not take credit for his musings that planted the

seed that grew into the specific topic I eventually landed on. This dissertation would not have been possible without their support.

Thank you to the Department of Epidemiology at Columbia University, including all of the faculty I learned from, and to Liliane Zaretsky and Elizabeth Ferrari for making the program as seamless as possible. And thank you especially to my fellow doctoral students, for your friendship and for humbling me with your talent and brilliance.

Finally, deepest gratitude and love to my family and friends for your support throughout the program and for reminding me what I was working for: my wife and daughter, Valerie and Sydney Palma; my parents, Antonio and Velinda Palma and Frank and Sue Chiong; my brother and sister-in-law, Karl Palma and Claudia Nain-Vera; and countless other friends and family in the many places I am lucky to call home.

## **DEDICATION**

To Mom, Dad and Karl, for their lifelong support that made me the person I am today;  
And to Valerie and Sydney Katherine, for their unconditional love and being my light on this  
journey.

## CHAPTER 1. INTRODUCTION

### 1.1. Background

#### *1.1.1. Cardiovascular disease risk behaviors in HIV*

In the era of antiretroviral therapy (ART), the survival of people living with HIV (PLWH) on treatment has approached that of the general population.<sup>1</sup> However, age-related chronic conditions such as cardiovascular disease (CVD) have become increasingly important contributors to their morbidity and mortality.<sup>2-5</sup> As a result, CVD prevention has become a top health priority for HIV-positive individuals. Current CVD prevention efforts aim to achieve routine screening and management of modifiable CVD risk factors,<sup>6</sup> centered around managing clinical risk factors (e.g., hypertension, dyslipidemia and diabetes) via direct pharmacological therapies and adjustment of HIV treatment regimens to reduce exposure to known cardiovascular ART toxicities.<sup>7-10</sup> However, there is growing recognition of the importance of behavioral risk factors for CVD. HIV treatment guidelines recommend “advising all HIV-positive persons to maintain a healthy lifestyle” by reducing tobacco smoking, hazardous alcohol use, and avoiding unhealthy diet and exercise habits.<sup>6</sup> Furthermore, modifying unhealthy lifestyle behaviors may be relatively inexpensive and provide benefits for overall health and well-being, making them favorable CVD prevention targets.<sup>11-13</sup>

CVD risk behaviors are highly prevalent among PLWH. The prevalence of smoking in HIV-positive populations is estimated to be between 30-60%, up to 2-3 times that of the general population.<sup>14-20</sup> The prevalence of hazardous alcohol use is between 1.5 to 2 times as high.<sup>21-25</sup> Diet and exercise behaviors have received less research attention, but some studies have shown, for example, higher levels of excessive dietary fat intake<sup>26</sup> and insufficient exercise<sup>27, 28</sup> in HIV-

positive persons as compared to uninfected controls. These findings often persist after controlling for known demographic and socioeconomic confounders and have been replicated across diverse populations, including those in both high and low resource settings.

### ***1.1.2. Does HIV itself influence CVD risk behaviors?***

The reasons for these differences have not been well-established, though alcohol use and smoking are typically considered to be antecedents of HIV acquisition, as they often co-occur in social situations that are conducive to risky sexual behavior.<sup>29</sup> As a result, alcohol use and smoking are most often examined as risk factors of HIV acquisition, as well as barriers to HIV testing, retention in HIV care and adherence to ART.<sup>30-33</sup> Less research attention has been placed on the opposite causal relationship—to examine whether HIV itself influences unhealthy lifestyle behaviors—despite the existence of plausible mechanisms through which this could occur.

HIV exhibits a wide array of adverse physiological and psychological manifestations.

Physiological manifestations include symptoms of HIV infection, such as fatigue,<sup>34</sup> pain due to HIV-related neuropathy (a consequence of infection and common side effect of HIV medications),<sup>35</sup> and muscle weakness, as well as outcomes associated with advanced HIV disease progression, such as physical dysfunction as measured by difficulties with activities of daily living (ADLs),<sup>36-38</sup> and even cognitive difficulties such as impaired memory and concentration.<sup>39</sup> In addition, a number of psychological manifestations of HIV exist, including elevated levels of depression and anxiety,<sup>40, 41</sup> and diminished subjective well-being as measured by self-reported quality of life and life satisfaction.<sup>42, 43</sup>

Taken together, these phenomena illustrate the diverse types of stress to which PLWH are exposed. Links between stress and CVD risk behavior engagement are well-established in the general population, and evidence suggests that HIV-related stress similarly contributes to health outcomes in HIV-positive populations.<sup>44-46</sup> However, prior studies have focused predominantly on clinical outcomes such as HIV disease progression and virologic or immunological function, rather than health behaviors.<sup>47</sup> In qualitative studies, PLWH are known to often report feeling overwhelmed by their diagnosis,<sup>48</sup> and adopting smoking or drinking behaviors to obtain relief from the physical symptoms of HIV, such as nausea and pain.<sup>48-51</sup> or distraction from the psychological stress of living with HIV.<sup>52-55</sup> Unhealthy dietary and sedentary lifestyles have not been studied extensively among PLWH, but stress-related eating and sedentary behaviors have been observed in other disease contexts, e.g., among breast cancer patients who experience discomforts from chemotherapy treatment and maintain fears of cancer recurrence.<sup>56</sup> In other words, HIV itself may have a causal influence on CVD risk behaviors via a stress-coping mechanism; yet, few existing studies have quantitatively tested this hypothesis.<sup>34, 57-59</sup>

## **1.2. Stress-coping theory**

Historically, the term stress has been conceptualized in various ways, including concepts as disparate as traumatic or impactful life events, subjective emotions, psychological symptoms (e.g., depression), and even biological markers (e.g., measured cortisol levels or autonomic nervous system activity). To clarify terminology, a brief note on stress-coping theory is needed. Stress-coping theories have an extensive history in multiple fields including medicine and psychology, in which the label *stress* carries different meanings.<sup>60</sup> Here, *stressor* is defined as any event or condition that imposes some physical or psychological demands on a person. *Stress* is defined as the individual's subjective experience of confronting these demands—that is, stress

is the *psychological response* to a perceived stressor. Lazarus' stress appraisal theory states that an individual who encounters a potential stressor undergoes the cognitive process of appraisal, where he/she evaluates whether the potential stressor constitutes a meaningful threat or harm and whether he/she has the resources to overcome it.<sup>61</sup> To illustrate, incurring an injury may cause anxiety in some individuals but may not in others, e.g., those who feel capable of achieving full recovery. The injury therefore may cause some but not all individuals to "feel stressed". Those who do may cope via different types of *coping responses*: cognitive (e.g., solution-seeking or avoidant thinking) and/or behavioral (e.g., removing the source of stress or engaging in distracting behaviors).

This theoretical framework can be applied to the current research question. Each of the physiological manifestations of HIV can be conceptualized as a potential source of stress (physiological stressor). To the extent that individuals engage in unhealthy CVD risk behaviors to cope with these stressors, they would act as mediators of a causal effect of HIV on CVD risk behaviors, explaining why HIV-positive individuals engage in higher rates of CVD risk behaviors than uninfected individuals. Some psychological phenomena, such as depressive symptoms, low self-reported quality of life and low life satisfaction, may serve as proxies for an individual's psychological experience of stress.<sup>62</sup> If so, these measures would also act as potential mediators of a causal effect of HIV on CVD risk behaviors.<sup>44, 46, 63-65</sup>

Further insights may be gleaned from a related stress-coping theory, Leventhal's self-regulation model of illness. Self-regulation theory states that individuals regulate their responses to health stressors, such as HIV, in accordance with their internal cognitive representation of it.<sup>66, 67</sup>

Among other things, this illness representation involves evaluating its anticipated *consequences*,

the *timeline* of those consequences, and the perceived *control* one has to change future outcomes.<sup>68</sup> These concepts underscore the importance of one's ability to make accurate predictions about the future as determinants of health prevention behaviors.<sup>69-72</sup> Within this theoretical framework, an individual's perceived life expectancy (PLE) may regulate how PLWH engage in CVD risk behaviors as a stress-coping response to their illness. Simply, PLE may be an effect modifier of the relationship between HIV and CVD risk behaviors.

### **1.3. Dissertation overview**

As HIV-infected populations survive and age in the era of ART, preventing CVD and other age-related comorbidities will be increasingly important.<sup>73</sup> Unhealthy lifestyle behaviors, which are prevalent and modifiable, represent potentially high-yield targets for intervention. Further research on the relationship between HIV and CVD risk behavior engagement, motivated by established stress-coping theories, may enhance understanding of the etiology of and inform prevention of CVD risk in this population.

This dissertation is organized into five chapters. Following this introductory chapter, three chapters are devoted to the three analytical aims of the dissertation: (aim 1) to systematically review the available evidence of the causal effects of HIV on CVD risk behaviors; (aim 2) to explore the patterns of CVD risk behavior engagement across stages of the HIV continuum and whether these relationships are explained by hypothesized mediators, as predicted by stress-coping theory; and (aim 3) to assess whether PLE modifies the relationships between HIV continuum stage and CVD risk behaviors. The final chapter synthesizes the findings of this dissertation and discusses implications for public health and directions for future research.

## 1.4. References

1. Palella, F.J., Jr., K.M. Delaney, A.C. Moorman, et al., *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.* N Engl J Med, 1998. **338**(13): p. 853-60.
2. Sackoff, J.E., D.B. Hanna, M.R. Pfeiffer, et al., *Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City.* Ann Intern Med, 2006. **145**(6): p. 397-406.
3. Clark, S.J., F.X. Gomez-Olive, B. Houle, et al., *Cardiometabolic disease risk and HIV status in rural South Africa: establishing a baseline.* BMC Public Health., 2015. **15:135**.(doi): p. 10.1186/s12889-015-1467-1.
4. Wada, N., L.P. Jacobson, M. Cohen, et al., *Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome-negative individuals followed simultaneously in long-term cohort studies, 1984-2008.* Am J Epidemiol, 2013. **177**(2): p. 116-25.
5. Hanna, D.B., C. Ramaswamy, R.C. Kaplan, et al., *Trends in Cardiovascular Disease Mortality Among Persons With HIV in New York City, 2001-2012.* Clin Infect Dis, 2016. **63**(8): p. 1122-1129.
6. European AIDS Clinical Society, *EACS guidelines for the treatment of adult HIV-positive persons.* 2017, EACS.
7. Dube, M.P., *Will statins be an effective anti-inflammatory intervention for prevention of cardiovascular disease in patients with HIV?* J Infect Dis, 2014. **209**(8): p. 1149-50.
8. Hicks, C., J. Currier, P. Sax, et al., *Current management challenges in HIV: tolerability of antiretrovirals and metabolic complications.* AIDS Patient Care STDS, 2003. **17**(5): p. 221-33.
9. Nduka, C., A. Sarki, O. Uthman, et al., *Impact of antiretroviral therapy on serum lipoprotein levels and dyslipidemias: a systematic review and meta-analysis.* Int J Cardiol, 2015. **199**: p. 307-18.
10. Manuel, O., R. Thiebaut, R. Darioli, et al., *Treatment of dyslipidaemia in HIV-infected persons.* Expert Opin Pharmacother, 2005. **6**(10): p. 1619-45.
11. Farley, J.E., C. Tudor, and C.R. Dennison, *Progress in prevention: improving cardiovascular risk management among human immunodeficiency virus-positive*

- individuals. *J Cardiovasc Nurs.*, 2010. **25**(4): p. 259-60. doi: 10.1097/JCN.0b013e3181e3aa98.
12. Grinspoon, S.K., C. Grunfeld, D.P. Kotler, et al., *State of the science conference: Initiative to decrease cardiovascular risk and increase quality of care for patients living with HIV/AIDS: executive summary.* *Circulation.*, 2008. **118**(2): p. 198-210. doi: 10.1161/CIRCULATIONAHA.107.189622. Epub 2008 Jun 19.
  13. Palar, K., T. Napoles, L.L. Hufstedler, et al., *Comprehensive and Medically Appropriate Food Support Is Associated with Improved HIV and Diabetes Health.* *J Urban Health.*, 2017. **94**(1): p. 87-99. doi: 10.1007/s11524-016-0129-7.
  14. Glass, T.R., C. Ungsedhapand, M. Wolbers, et al., *Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study.* *HIV Med*, 2006. **7**(6): p. 404-10.
  15. Tesoriero, J.M., S.M. Gieryic, A. Carrascal, et al., *Smoking among HIV positive New Yorkers: prevalence, frequency, and opportunities for cessation.* *AIDS Behav*, 2010. **14**(4): p. 824-35.
  16. Lifson, A.R. and H.A. Lando, *Smoking and HIV: prevalence, health risks, and cessation strategies.* *Curr HIV/AIDS Rep*, 2012. **9**(3): p. 223-30.
  17. Mdodo, R., E.L. Frazier, S.R. Dube, et al., *Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys.* *Ann Intern Med*, 2015. **162**(5): p. 335-44.
  18. Weinberger, A.H., P.H. Smith, A.P. Funk, et al., *Sex Differences in Tobacco Use Among Persons Living With HIV/AIDS: A Systematic Review and Meta-Analysis.* *J Acquir Immune Defic Syndr.*, 2017. **74**(4): p. 439-453. doi: 10.1097/QAI.0000000000001279.
  19. Shiau, S., S.M. Arpadi, M.T. Yin, et al., *Patterns of drug use and HIV infection among adults in a nationally representative sample.* *Addict Behav.*, 2017. **68:39-44**.(doi): p. 10.1016/j.addbeh.2017.01.015. Epub 2017 Jan 7.
  20. Mdege, N.D., S. Shah, O.A. Ayo-Yusuf, et al., *Tobacco use among people living with HIV: analysis of data from Demographic and Health Surveys from 28 low-income and middle-income countries.* *Lancet Glob Health.*, 2017. **5**(6): p. e578-e592. doi: 10.1016/S2214-109X(17)30170-5.
  21. Crane, H.M., M.E. McCaul, G. Chander, et al., *Prevalence and Factors Associated with Hazardous Alcohol Use Among Persons Living with HIV Across the US in the Current Era of Antiretroviral Treatment.* *AIDS Behav*, 2017. **11**(10): p. 017-1740.

22. Ikeda, M.L., N.T. Barcellos, P.R. Alencastro, et al., *Alcohol Drinking Pattern: A Comparison between HIV-Infected Patients and Individuals from the General Population*. PLoS One., 2016. **11**(6): p. e0158535. doi: 10.1371/journal.pone.0158535. eCollection 2016.
23. Fisher, J.C., H. Bang, and S.H. Kapiga, *The association between HIV infection and alcohol use: a systematic review and meta-analysis of African studies*. Sex Transm Dis, 2007. **34**(11): p. 856-63.
24. Galvan, F.H., E.G. Bing, J.A. Fleishman, et al., *The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study*. J Stud Alcohol., 2002. **63**(2): p. 179-86.
25. Kelso, N.E., D.S. Sheps, and R.L. Cook, *The association between alcohol use and cardiovascular disease among people living with HIV: a systematic review*. Am J Drug Alcohol Abuse, 2015. **41**(6): p. 479-88.
26. Joy, T., H.M. Keogh, C. Hadigan, et al., *Dietary fat intake and relationship to serum lipid levels in HIV-infected patients with metabolic abnormalities in the HAART era*. AIDS., 2007. **21**(12): p. 1591-600. doi: 10.1097/QAD.0b013e32823644ff.
27. Schafer, J., J. Young, A. Calmy, et al., *High prevalence of physical inactivity among patients from the Swiss HIV Cohort Study*. AIDS Care., 2017. **29**(8): p. 1056-1061. doi: 10.1080/09540121.2016.1274016. Epub 2017 Jan 5.
28. Schuelter-Trevisol, F., F.H. Wolff, P.R. Alencastro, et al., *Physical activity: do patients infected with HIV practice? How much? A systematic review*. Curr HIV Res., 2012. **10**(6): p. 487-97.
29. Shuper, P.A., M. Neuman, F. Kanteres, et al., *Causal considerations on alcohol and HIV/AIDS--a systematic review*. Alcohol Alcohol., 2010. **45**(2): p. 159-66. doi: 10.1093/alcalc/agg091. Epub 2010 Jan 8.
30. Schneider, M., M. Chersich, M. Temmerman, et al., *The impact of alcohol on HIV prevention and treatment for South Africans in primary healthcare*. Curationis., 2014. **37**(1): p. 1137. doi: 10.4102/curationis.v37i1.1137.
31. Shuter, J. and S.L. Bernstein, *Cigarette smoking is an independent predictor of nonadherence in HIV-infected individuals receiving highly active antiretroviral therapy*. Nicotine Tob Res, 2008. **10**(4): p. 731-6.

32. Conserve, D., G. King, A. Turo, et al., *Cigarette smoking and alcohol use as predictors of HIV testing in the United States: results from the 2010 National Health Interview Survey*. *AIDS Care*, 2014. **26**(7): p. 842-9.
33. Marshall, M.M., M.C. McCormack, and G.D. Kirk, *Effect of cigarette smoking on HIV acquisition, progression, and mortality*. *AIDS Educ Prev.*, 2009. **21**(3 Suppl): p. 28-39. doi: 10.1521/aeap.2009.21.3\_supp.28.
34. Regan, S., J.B. Meigs, S.K. Grinspoon, et al., *Determinants of Smoking and Quitting in HIV-Infected Individuals*. *PLoS One.*, 2016. **11**(4): p. e0153103. doi: 10.1371/journal.pone.0153103. eCollection 2016.
35. Ferrari, S., S. Vento, S. Monaco, et al., *Human immunodeficiency virus-associated peripheral neuropathies*. *Mayo Clin Proc.*, 2006. **81**(2): p. 213-9. doi: 10.4065/81.2.213.
36. Rosen, S., M. Ketlhapile, I. Sanne, et al., *Differences in normal activities, job performance and symptom prevalence between patients not yet on antiretroviral therapy and patients initiating therapy in South Africa*. *Aids*, 2008. **22 Suppl 1**: p. S131-9.
37. O'Brien, K.K., A.M. Bayoumi, C. Strike, et al., *Exploring disability from the perspective of adults living with HIV/AIDS: development of a conceptual framework*. *Health Qual Life Outcomes*, 2008. **6**: p. 76.
38. Schrack, J.A., L.P. Jacobson, K.N. Althoff, et al., *Effect of HIV-infection and cumulative viral load on age-related decline in grip strength*. *Aids*, 2016. **30**(17): p. 2645-2652.
39. Seider, T.R., X. Luo, A. Gongvatana, et al., *Verbal memory declines more rapidly with age in HIV infected versus uninfected adults*. *J Clin Exp Neuropsychol*, 2014. **36**(4): p. 356-67.
40. Dube, B., T. Benton, D.G. Cruess, et al., *Neuropsychiatric manifestations of HIV infection and AIDS*. *J Psychiatry Neurosci*, 2005. **30**(4): p. 237-46.
41. Hinkin, C.H., S.A. Castellon, J.H. Atkinson, et al., *Neuropsychiatric aspects of HIV infection among older adults*. *J Clin Epidemiol*, 2001. **54 Suppl 1**: p. S44-52.
42. Reis, A.C., M.N. Guerra, and L.M. Lencastre, *Treatment adherence and subjective well-being in HIV/AIDS infection*. *AIDS Care*, 2013. **25**(12): p. 1604-11.
43. Greeff, M., L.R. Uys, D. Wantland, et al., *Perceived HIV stigma and life satisfaction among persons living with HIV infection in five African countries: a longitudinal study*. *Int J Nurs Stud.*, 2010. **47**(4): p. 475-86. doi: 10.1016/j.ijnurstu.2009.09.008. Epub 2009 Oct 24.

44. Corless, I.B., J. Voss, A.J. Guarino, et al., *The impact of stressful life events, symptom status, and adherence concerns on quality of life in people living with HIV*. J Assoc Nurses AIDS Care., 2013. **24**(6): p. 478-90. doi: 10.1016/j.jana.2012.11.005. Epub 2013 Mar 7.
45. Rod, N.H., M. Gronbaek, P. Schnohr, et al., *Perceived stress as a risk factor for changes in health behaviour and cardiac risk profile: a longitudinal study*. J Intern Med., 2009. **266**(5): p. 467-75. doi: 10.1111/j.1365-2796.2009.02124.x. Epub 2009 Apr 23.
46. Schneiderman, N., G. Ironson, and S.D. Siegel, *Stress and health: psychological, behavioral, and biological determinants*. Annu Rev Clin Psychol, 2005. **1:607-28**.(doi): p. 10.1146/annurev.clinpsy.1.102803.144141.
47. Weinstein, T.L. and L. Xiaoming, *The relationship between stress and clinical outcomes for persons living with HIV/AIDS: a systematic review of the global literature*. AIDS Care, 2016. **28**(2): p. 160-169.
48. Reynolds, N.R., *Cigarette smoking and HIV: more evidence for action*. AIDS Educ Prev., 2009. **21**(3 Suppl): p. 106-21. doi: 10.1521/aeap.2009.21.3\_supp.106.
49. Grover, K.W., A. Gonzalez, and M.J. Zvolensky, *HIV symptom distress and smoking outcome expectancies among HIV+ smokers: a pilot test*. AIDS Patient Care STDS., 2013. **27**(1): p. 17-21. doi: 10.1089/apc.2012.0333.
50. Tsui, J.I., D.M. Cheng, S.M. Coleman, et al., *Pain and Risk Behaviors Among HIV-Infected Persons in St. Petersburg, Russia*. AIDS Behav., 2017. **21**(6): p. 1775-1781. doi: 10.1007/s10461-016-1593-5.
51. Weinberger, A.H., E.K. Seng, J.W. Ditre, et al., *Perceived interrelations of pain and cigarette smoking in a sample of adult smokers living with HIV/AIDS*. Nicotine Tob Res, 2018. **31**(4830708).
52. Elliott, J.C., E. Aharonovich, A. O'Leary, et al., *Drinking motives among HIV primary care patients*. AIDS Behav., 2014. **18**(7): p. 1315-23. doi: 10.1007/s10461-013-0644-4.
53. Akhtar-Khaleel, W.Z., R.L. Cook, S. Shoptaw, et al., *Trends and Predictors of Cigarette Smoking Among HIV Seropositive and Seronegative Men: The Multicenter Aids Cohort Study*. AIDS Behav., 2016. **20**(3): p. 622-32. doi: 10.1007/s10461-015-1099-6.
54. Webb, M.S., P.A. Venable, M.P. Carey, et al., *Cigarette smoking among HIV+ men and women: examining health, substance use, and psychosocial correlates across the smoking spectrum*. J Behav Med., 2007. **30**(5): p. 371-83. Epub 2007 Jun 15.

55. Garey, L., J. Bakhshaie, C. Sharp, et al., *Anxiety, depression, and HIV symptoms among persons living with HIV/AIDS: the role of hazardous drinking*. *AIDS Care*, 2015. **27**(1): p. 80-5. doi: 10.1080/09540121.2014.956042. Epub 2014 Sep 16.
56. Kelly, K.M., R. Bhattacharya, S. Dickinson, et al., *Health Behaviors Among Breast Cancer Patients and Survivors*. *Cancer Nurs.*, 2015. **38**(3): p. E27-34. doi: 10.1097/NCC.000000000000167.
57. Kobau, R., M.A. Safran, M.M. Zack, et al., *Sad, blue, or depressed days, health behaviors and health-related quality of life: Behavioral Risk Factor Surveillance System, 1995-2000*. *Health Qual Life Outcomes*, 2004. **2**: p. 40.
58. Nicholas, P.K., J.G. Voss, I.B. Corless, et al., *Unhealthy behaviours for self-management of HIV-related peripheral neuropathy*. *AIDS Care.*, 2007. **19**(10): p. 1266-73.
59. Park, C.L. and M.O. Iacocca, *A stress and coping perspective on health behaviors: theoretical and methodological considerations*. *Anxiety Stress Coping*, 2014. **27**(2): p. 123-37. doi: 10.1080/10615806.2013.860969. Epub 2013 Dec 10.
60. Engel, B.T., *Stress is a noun! No, a verb! No, an adjective.*, in *Stress and coping*, T.M. Field, P.M. McCabe, and N. Schneiderman, Editors. 1985, Erlbaum: Hillsdale, NJ. p. 3-12.
61. Lazarus, R.S. and S. Folkman, *Stress, appraisal, and coping*. 1984, New York: Springer.
62. McGrath, J.E., *Methodological problems in research on stress*, in *Achievement, Stress, and Anxiety*, H.W. Krohne and L. Laux, Editors. 1982, Hemisphere: Washington, DC. p. 19-48.
63. Hamarat, E., D. Thompson, K.M. Zabrocky, et al., *Perceived stress and coping resource availability as predictors of life satisfaction in young, middle-aged, and older adults*. *Exp Aging Res.*, 2001. **27**(2): p. 181-96. doi: 10.1080/036107301750074051.
64. Hannaford, E., F. Moore, and F.J. Macleod, *What a difference a year makes: comparing relationships between stressful life events, mood and life satisfaction among older adults, and their working-age counterparts*. *Aging Ment Health*, 2017. **11**: p. 1-8.
65. Kessler, R.C., *The effects of stressful life events on depression*. *Annu Rev Psychol*, 1997. **48**:191-214.(doi): p. 10.1146/annurev.psych.48.1.191.
66. Leventhal, H., I. Brissette, E.A. Leventhal, et al., *The common sense model of self-regulation of health and illness*, in *The Self-Regulation of Health and Illness Behavior*. 2003, Routledge: London. p. 42-65.

67. Leventhal, H., Y. Benyamini, S. Brownlee, et al., *Illness representations and coping with health threats*, in *Handbook of psychology and health*, A. Baum, S.E. Taylor, and J.E. Singer, Editors. 1997, Lawrence Erlbaum: Hillsdale, NJ.
68. Diefenebach, M.A. and H. Leventhal, *The common-sense model of illness representation: Theoretical and practical considerations*. *Journal of Social Distress and the Homeless*, 1996. **5**: p. 11-38.
69. Mezuk, B., S. Ratliff, J.B. Concha, et al., *Stress, self-regulation, and context: Evidence from the Health and Retirement Survey*. *SSM Popul Health.*, 2017. **3**:455-463.(doi): p. 10.1016/j.ssmph.2017.05.004. Epub 2017 May 6.
70. Munro, S., E. Dinatale, S. Hartley, et al., *Barriers and Health Beliefs Related to Weight Management Among Veterans With Human Immunodeficiency Virus*. *Mil Med.*, 2017. **182**(1): p. e1596-e1602. doi: 10.7205/MILMED-D-16-00086.
71. Browning, K.K., M.E. Wewers, A.K. Ferketich, et al., *The Self-regulation Model of Illness applied to smoking behavior in lung cancer*. *Cancer Nurs.*, 2009. **32**(4): p. E15-25. doi: 10.1097/NCC.0b013e3181a0238f.
72. Byrne, M., J. Walsh, and A.W. Murphy, *Secondary prevention of coronary heart disease: patient beliefs and health-related behaviour*. *J Psychosom Res.*, 2005. **58**(5): p. 403-15. doi: 10.1016/j.jpsychores.2004.11.010.
73. Global Burden of Disease Study 2013 Collaborators, *Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013*. *Lancet*, 2015. **386**(9995): p. 743-800.

## **CHAPTER 2. DOES HIV CAUSE CARDIOVASCULAR DISEASE RISK BEHAVIORS? A SYSTEMATIC REVIEW OF EVIDENCE ACROSS THE HIV CONTINUUM**

### **2.1. Abstract**

**Background:** Studies have demonstrated that cardiovascular disease (CVD) risk behaviors (smoking, hazardous alcohol use, poor dietary habits and sedentary behaviors) are more prevalent among people living with HIV (PLWH) as compared to the general population. While the reasons for these differences are not well-established, qualitative studies suggest that PLWH often turn to unhealthy behaviors to cope with the stress of living with their illness, including the adverse physiological symptoms of HIV infection, the psychological stress of being aware of one's HIV status, and the physiological and psychological impacts of being on HIV treatment. These observations suggest that being HIV-positive may have a causal influence on CVD risk behaviors and that these causal effects likely differ across stages of the HIV continuum. However, few quantitative studies to date have been conducted specifically to test whether being HIV-positive causes increased CVD risk behaviors. In this study, we systematically reviewed the available literature in support of causal effects of HIV continuum stage on CVD risk behaviors.

**Methods:** Pubmed, Web of Science, EMBASE and PsycINFO databases were searched to identify all peer-reviewed articles published between 2000-2018 that compared CVD risk behaviors by HIV continuum stage, defined as either HIV infection status, awareness, treatment or immune/virologic recovery. Articles were eligible for inclusion if they assessed relationships between HIV continuum stage (four groups: HIV-negative, HIV-positive but unaware of HIV status, HIV-positive and aware of HIV status but not on treatment, and HIV-positive on treatment) and any CVD risk behavior. We reviewed studies for methodological quality, observed findings, and variability for each HIV continuum stage and across demographic groups.

**Results:** We included 81 articles in this review, representing 30 analyses on smoking, 54 on alcohol use, 2 on dietary behaviors and 6 on sedentary behaviors; nineteen (19%) of these were longitudinal. We found that smoking and alcohol use were the ones most commonly studied (33% and 58% of available analyses, respectively). Studies used widely disparate measures and sampling methods, and observed findings were widely inconsistent across studies. Generally, results support positive associations between HIV infection and awareness status and increased smoking and alcohol use, and protective associations between HIV treatment and immune/viral recovery and decreased smoking and alcohol use. Findings for dietary and sedentary behaviors were less clear due to insufficient sample size.

**Discussion:** This review showed that most studies were cross-sectional and that there was wide variability in methods used across studies. The paucity of longitudinal studies reflects methodological difficulties and the historical tendency to conceptualize CVD risk behaviors, particularly smoking and alcohol, as predictors, rather than consequences, of HIV acquisition, awareness of HIV infection after testing and treatment. Future research is required to examine the effects of HIV continuum stage on CVD risk behaviors directly in order to strengthen causal claims and to assess underlying mechanisms.

## 2.1. Introduction

People living with HIV (PLWH) experience excess cardiovascular disease (CVD)-related morbidity and mortality compared to the general population, due to, among other things, higher rates of several CVD risk behaviors, including tobacco smoking, hazardous alcohol use, poor diet and sedentary behaviors.<sup>1</sup> Smoking prevalence is estimated to be between 30-60%, up to 2-3 times that of the general population,<sup>2-9</sup> and hazardous alcohol use is between 1.5 to 2 times as high.<sup>10-14</sup> Poor diet and sedentary behaviors in this population are less well-understood, but some studies have shown, for example, higher levels of dietary fat intake<sup>15</sup> and insufficient exercise<sup>16, 17</sup> among HIV-positive persons than uninfected controls. These findings often persist after controlling for known demographic and socioeconomic confounders and have been replicated across diverse settings.

The reasons for these differences have not been fully established, in part because CVD risk behaviors may be both antecedents and consequences of HIV. Most existing research among PLWH has focused on smoking and alcohol use, treating them as risk factors of HIV acquisition, as well as common barriers to HIV testing, HIV care attendance, and antiretroviral treatment (ART) adherence.<sup>18-21</sup> Smoking and alcohol use are known to occur in social situations that are conducive to risky sexual behavior.<sup>22</sup> However, growing qualitative evidence also shows that PLWH often report seeking unhealthy behaviors as a means of coping with their illness,<sup>23, 24</sup> a behavioral stress-coping response that occurs even among those who recognize the harms and express the desire to change.<sup>25-27</sup>

Quantitative evidence for the causal influence of HIV infection on CVD risk behaviors is currently lacking, partly reflecting a historical tendency for researchers to focus efforts on HIV

prevention. More importantly, the quantitative evidence that does exist is inconsistent. This is likely a result of some key methodological difficulties. First, lifestyle behaviors are difficult to measure, as they are most readily assessed by self-report and can be prone to social desirability bias. Second, temporality is not easily established as they are, by definition, highly time-variant and few studies examine long-term CVD risk behavior patterns as an outcome of interest among HIV-positive populations. Given the high costs required to sufficiently follow individuals prospectively and observe their long-term behaviors, cross-sectional studies are naturally the most commonly employed study designs on this topic. Third, most studies are conducted in clinic-based or convenience samples, which is a known source of selection bias.<sup>28</sup> Fourth, despite the fact that plausible stress-coping mechanisms have been identified in the qualitative literature, few investigators explicitly articulate the underlying mechanisms when conducting quantitative studies. This results in ambiguity regarding how variables are selected and measured, what role they are hypothesized to play, and ultimately how to interpret results. Specifically, if a stress-coping hypothesis is true, individuals who use unhealthy behaviors to “cope with HIV” may be responding to the physical symptoms of HIV,<sup>29-31</sup> the psychological toll of receiving a positive HIV diagnosis,<sup>32-34</sup> or the physical and/or psychological consequences of being on HIV treatment.<sup>17</sup> HIV, as an exposure, is measured inconsistently across studies; some studies compare individuals without HIV infection to those with HIV infection, regardless of whether they are aware of their status, while other studies compare self-reported HIV-positives with self-reported negatives, without distinguishing actual HIV infection status, and some studies compare treated versus untreated individuals. Observed findings would be expected to vary depending on the measure used i.e., across different stages of the HIV continuum. Furthermore, it is possible that individuals within each of these stages of the HIV continuum may have different effects

across people or time. Being aware of one's HIV status, for example, may be a positive health motivator for some individuals but may instead be a source of anxiety for others, or may simply have decreasing influence as time passes. The complex motivations for health behaviors among PLWH are firmly supported within established theories of health behavior and remain an area of active research.<sup>35, 36</sup>

Due to these gaps, there is no clear consensus regarding the effects of HIV on CVD risk behaviors. Nonetheless, HIV care and treatment guidelines recommend that clinicians routinely advise all HIV-positive persons to maintain healthy behaviors as a key component of CVD prevention.<sup>37</sup> Better understanding of the unique motivations for unhealthy behaviors, and in particular the influence of HIV-positive status itself, is crucial to these efforts.

In this study, we systematically reviewed the available quantitative evidence, with particular attention to differences across HIV continuum stages and over time. We also examined the quality of evidence with respect to measurement and sampling, as well as variability in findings across demographic groups and settings.

## **2.2. Methods**

PubMed, Web of Science, EMBASE and PsycINFO databases were searched for all studies that examined the relationship between HIV continuum stage and any of the four CVD risk behaviors (full search term details are reported in Appendix Table 5.1). We also scanned the reference lists of selected articles for additional relevant articles missed in the initial search. For this analysis, smoking and alcohol use included any current or recent measures of smoking tobacco products or alcoholic beverages, respectively, exclusive of illicit drug use. Due to the absence of standard

definitions of dietary or sedentary behaviors, all measures were considered eligible for inclusion. Studies must have been conducted among adults (age 15 and older) and published in English since 2000 (i.e., after combination ART became widely available). Non-empirical papers (reviews and commentaries), qualitative studies, and studies designed to test CVD risk behavior modification intervention (e.g., counseling, peer support, education, and/or pharmacologic therapies that target the behavior of interest) were excluded.

We prioritized longitudinal studies with measures of behavior change within the same individual over time. These consisted primarily of two types. Analyses with measures of self-reported behavior change before versus after a change in HIV continuum stage were classified as *pre/post behavior change* analyses (e.g., proportion of prior smokers who quit after receiving their HIV diagnosis). In contrast, we classified analyses with repeated measures of the behavior over time as *trajectory* analyses (e.g., smoking prevalence over time among HIV-positive vs. HIV-negative groups at baseline). The key difference is the time at which HIV continuum stage was measured relative to when the CVD risk behavior was measure. After an initial review returned relatively few longitudinal studies with repeated measures of a CVD risk behavior over time, we expanded the search to include cross-sectional analyses (i.e., those that compared behavior prevalence at one time between groups of individuals at different HIV continuum stages), regardless of the direction of causation hypothesized by the authors.<sup>a</sup> Exceptions were made to exclude studies

---

<sup>a</sup> Some analyses were conducted within longitudinal cohorts but utilized only cross-sectional data , e.g., from the baseline or most recent study visit. These were considered cross-sectional analyses for this review.

where the CVD risk behavior was known to occur prior to HIV acquisition(e.g., alcohol use as a risk factor for unprotected sex among HIV-positive versus HIV-negative groups).

After identifying potentially eligible studies, relevant information was downloaded into EndNote and reviewed by author, year and title to remove duplicates. Titles were initially screened to identify studies eligible for inclusion; then two independent reviewers, AP and DH<sup>b</sup>, screened abstracts to confirm eligibility and discussed discrepancies to obtain consensus. Finally, the full text of each article was reviewed to confirm eligibility, and extract and summarize study characteristics. Extracted data included author(s), publication year, geographic region, sample size, sampling method, variable measurement (i.e., self-report or biomarker, time frame, etc.), covariates adjusted in the analysis (if any), and observed findings. We synthesized results and described the availability and quality of evidence for each CVD risk behavior by HIV continuum stage.

### **2.3. Results**

Figure 2.1 displays the systematic review flowchart. The initial search yielded a total of 3,835 titles. After removing duplicates, we screened titles of 2,939 articles and deemed 2,692 as irrelevant. The abstracts of the remaining 247 articles were reviewed, after which 104 were retained for full text review. Twenty-three were further excluded based on full-text review for the following reasons: no comparison made across HIV continuum stage (n=15), no available full text article (n=3), no appropriate measure of CVD risk behavior (n=3), study tested a CVD

---

<sup>b</sup> Anton Palma and Debbie Huang

risk behavior modification intervention (n=1), and study conducted prior to 2000 (n=1). Several articles investigated multiple CVD risk behaviors and were treated as multiple analyses for the purpose of this review. Ultimately, we included in the review 81 published articles, representing a total of 94 unique analyses: 30 on smoking,<sup>5, 7, 8, 36, 38-63</sup> 54 on alcohol use,<sup>7, 10, 11, 35, 39, 51, 57, 58, 60, 64-108</sup> two on dietary behaviors,<sup>47, 109</sup> and six on sedentary behaviors<sup>47, 52, 57, 64, 110, 111</sup>. Eighteen (19%) of these were longitudinal: seven on smoking,<sup>36, 38, 40, 47, 53, 59, 62</sup> nine on alcohol use,<sup>35, 66, 67, 74, 81, 83, 88, 91, 108</sup> two on dietary behaviors,<sup>47, 109</sup> and one on sedentary behaviors<sup>47</sup>.

Extracted data from all longitudinal analyses are reported separately by CVD risk behavior in Tables 2.1-2.4 (data for all cross-sectional analyses are in Appendix Tables 5.2-5.5). Alcohol use and smoking were the most frequently studied of the four outcomes (58% and 33% of longitudinal analyses, respectively). Overall, the majority of longitudinal analyses were conducted in hospital- or clinic-based settings (13/18, 72%), with a few exceptions conducted in population-based (n=2, 11%)<sup>35, 36</sup> or community-based/respondent-driven samples (n=3, 17%)<sup>59, 64, 81</sup>. The distribution of sampling methods was similar among the cross-sectional analyses (Table 2.5).

### **2.3.1. Smoking**

Of the seven available longitudinal analyses on smoking (Table 2.1), three assessed changes in smoking pre/post HIV diagnosis. Among those who smoked previously, the estimates of prevalence of self-reported cessation post HIV diagnosis ranged between 19% to 49%.<sup>36, 47, 59</sup> Three analyses used group-based trajectory modeling on repeated smoking measures data to assess differences in smoking trajectories by baseline HIV status; these analyses found no significant effect of HIV-positive status on subsequent smoking trajectories (median follow-up

ranged 4-9 years, with assessments every 6 or 12 months).<sup>38, 53, 59</sup> Generally, findings from trajectory analyses showed little variability in long-term smoking patterns; in a study of 6,577 men who have sex with men (MSM) in the established Multicenter AIDS Cohort Study (MACS), 90% of participants were characterized as having no change in their smoking status throughout the entire follow-up period.<sup>38</sup> Two analyses assessed smoking changes pre/post HIV care initiation; findings suggested that care initiation was associated with modest short-term improvements in smoking.<sup>40, 62</sup> Of note, one study found that while intention to quit smoking increased three months after initiating care, these trends diminished from 3 to 12 months. Intention to quit was also associated with advanced HIV disease, as measured by CD4+ cell count and viral load (VL), but actual achievement of smoking cessation (i.e., confirmed by expired CO) was not.<sup>62</sup>

Twenty-three cross-sectional analyses on smoking were reviewed (Appendix Table 5.2). These studies were conducted in a wide variety of demographic groups; however, most (15/23, 65%) were conducted in high-resource settings, such as the US, Canada, Europe or Australia.<sup>5, 7, 39, 41-44, 46, 48, 49, 52, 56, 57, 60, 61, 63</sup> Three analyses (13%) used biomarker measures (e.g., blood cotinine or expired CO).<sup>44, 50, 62</sup> Overall, the results from these cross-sectional analyses showed that being HIV-infected was generally associated with higher smoking prevalence. Similarly, being aware of one's HIV-positive status was generally associated with higher smoking prevalence. However, some studies comparing self-reported HIV-positives to self-reported HIV-negatives included only truly HIV-infected individuals while others included HIV-uninfected individuals as well; thus, results cannot be easily compared even among multiple studies ostensibly testing the effects of HIV awareness due to varying reference groups. Conversely, we found mixed evidence for the

association between HIV treatment and smoking prevalence. Last, HIV immune/viral recovery was generally associated with reduced smoking prevalence (Appendix Table 5.6).

### **2.3.2. Alcohol use**

Eight longitudinal analyses on alcohol use were reviewed (Table 2.2). In three analyses, conducted in China and the U.S., up to 46% of participants who received their HIV diagnosis reported pre/post decreases in the amount of alcohol used.<sup>35, 81, 108</sup> However, almost half also reported no change and as much as 19% of the population increased drinking instead.<sup>35, 108</sup> Findings were dependent upon the target population; in a study of female sex workers (FSW) in Miami, US, HIV-positive participants were almost twice as likely as HIV-negative participants to reduce their alcohol use after receiving HIV testing.<sup>81</sup> Three analyses examined the relationship between ART status and long-term alcohol consumption using longitudinal clinic visit data and found no significant associations.<sup>66, 74, 91</sup> Finally, a few trajectory analyses found that ART non-adherence and HIV disease progression were associated with elevated alcohol use, compared to those who were ART adherent and those who did not have disease progression, respectively (median follow-up times ranged from 1 to 9 years).<sup>67, 83, 88</sup>

The remaining 49 cross-sectional analyses on alcohol are described in Appendix Table 5.3.

Unlike for smoking, a majority of studies on alcohol use were conducted outside of North America/Europe/Australia.<sup>11, 35, 51, 58, 64, 69, 72, 73, 76-78, 82, 84, 85, 87, 89, 92, 93, 95, 96, 98-100, 103-107</sup> Only one available study had biomarker measures (blood levels of phosphatidylethanol).<sup>88</sup> Findings were inconsistent across studies. For example, among 26 studies comparing alcohol use by HIV infection status, 12 showed positive associations (i.e., HIV-positive persons drank more), 7 were negative and 7 were null.

### **2.3.3. Dietary behavior**

Dietary behavior received the least research attention of the four CVD risk behaviors, with only two available longitudinal studies (Table 2.3).<sup>47, 109</sup> One study used repeated measures of dietary intake among a sample of HIV-positive men, based on 3-day food diaries at study visits. Cluster analysis was used to classify participants into three general dietary patterns, which were compared on health outcomes including CD4 count and viral load. No meaningful differences in these outcomes were observed between groups.<sup>109</sup> In contrast, another study used measured changes in self-rated healthy diet pre/post HIV diagnosis, finding that 60.4% of persons in HIV care reported making healthy changes to their diet following their HIV diagnosis.<sup>47</sup> No relevant cross-sectional studies of dietary behavior were found in the review (Appendix Table 5.4).

### **2.3.4. Sedentary behavior**

The same study above included the only available longitudinal analysis of sedentary behavior. Participants self-reported whether their engagement in “regular exercise” changed after receiving their HIV diagnosis; results indicated that 43.6% reported newly engaging in “regular exercise” after receiving their HIV diagnosis (Table 2.4).<sup>47</sup> The other five analyses were cross-sectional and used highly disparate measures of sedentary behavior; three defined sedentary behavior using measures of time spent engaging in physical activity (e.g., vigorous or moderate activity)<sup>52, 57, 110</sup>, and two measured self-reported participation in exercise or sports programs.<sup>64, 111</sup> Results largely showed no association between HIV continuum stage and any measure of sedentary behavior. Allen et al. found that high ART adherence was associated with participation in an exercise program (Appendix Table 5.5).<sup>64</sup>

## 2.4. Discussion

In this study, we aimed to systematically review the available literature on the effects of being in various stages of the HIV continuum on CVD risk behaviors. Of the four CVD risk behaviors we reviewed, smoking and alcohol use received the most research attention. Among the available studies on smoking and alcohol use, we observed that outcomes were compared across each of the HIV continuum stages, but that there was substantial variability in study designs and reported results (Table 2.5). The evidence generally supports positive associations between being HIV-infected versus HIV-uninfected and elevated smoking and alcohol risk, and positive associations between being aware versus unaware of one's HIV-positive status and elevated smoking and alcohol risk. In contrast, being on HIV treatment was generally associated with reduced smoking and alcohol risk. Dietary and sedentary behaviors received little research attention, thus there is insufficient evidence to draw any conclusions (Table 2.6). Importantly, despite the fact that stress-coping hypotheses are commonly cited as a plausible underlying mechanism, almost none of the available studies directly tested whether stress explained the observed associations, with few exceptions.<sup>99</sup> Some authors acknowledged the role of stress-coping implicitly by controlling for various measures of stress (e.g., physical or psychological symptoms of HIV) as covariates in the analytical model. However, since stress-coping hypotheses were rarely of primary interest, comparisons with results after adjusting for these specific variables were not presented.

It is worth noting that findings varied even across analyses ostensibly focused on the same HIV continuum stage-CVD risk behavior relationship. It is possible that this variability signifies true differences in effects across populations. However, several likely methodological sources of variability should be considered. A major consideration is differences in the time-frame of observation. This was most clearly illustrated in the study of smoking trends among HIV-

positive patients initiating HIV care, which found sharp decreases in smoking behavior three months after HIV care initiation that tapered off during follow-up from 3 to 12 months.<sup>62</sup> Similar patterns were evident with respect to HIV diagnosis, where reductions in smoking and alcohol use pre/post HIV diagnosis decreased as the time since diagnosis increased.<sup>35, 36</sup> In other words, those who made healthy behavior changes after diagnosis were increasingly likely to relapse over longer periods of follow-up. In a similar vein, the findings from analyses using pre/post behavior change measures were generally not consistent with those on behavior trajectories. Whereas healthy behavior change was found to be commonplace among pre/post measures, trajectory analyses found long-term behavior change to be rare, often characterizing the overwhelming majority of participants as, e.g., persistent non-smokers or persistent heavy smokers.<sup>38</sup> These trends may also be explained by time-frame of observation, since studies of pre/post behavior change typically measured behaviors more proximate to the event of interest, either HIV diagnosis or treatment initiation. It is known that these HIV care milestones heighten the salience of one's own health vulnerabilities and increase contact with the health system, each of which could impact health behavior motivations;<sup>62</sup> however, these phenomena would exhibit a recency effect as individuals become accustomed to their new circumstances.<sup>46, 62</sup> Whether these HIV care milestones constitute “teachable moments” that are more amenable to behavior modification intervention remains an area of active research.<sup>62, 112</sup>

Further uncertainty stems from ambiguity in how HIV continuum stage was defined, as a result of inadequate measurement or insufficient information provided. For example, HIV care or ART use status were often included as “covariates” in analytic models of behaviors by HIV status, but they may in fact be important determinants themselves. Indeed, observed associations varied by whether comparison groups captured differences in HIV infection, awareness of HIV infection or

treatment status. Disaggregating fully by HIV continuum stage would have helped clarify these differences, though some aspects are inevitably difficult to ascertain, such as determining time of HIV acquisition among persons newly diagnosed with HIV.

Lastly, measuring lifestyle behaviors is inherently imprecise. CVD risk behaviors were most often self-reported; however this limitation may be fundamentally unavoidable for outcomes such as dietary intake for which no biomarker measures are currently available. Nonetheless, the few studies of smoking and alcohol that used biomarker confirmation did not yield qualitatively different results from those that did not.<sup>50, 62</sup> Relatedly, detailed data such as the frequency or magnitude of a behavior was occasionally omitted or collapsed to binary variables in order to simplify data collection and analysis. Studies may yield different results if the granularity of measurement is important, e.g., if stress due to receiving an HIV diagnosis causes increases in binge drinking but does not cause increases in non-binge drinking. A number of studies used validated measures for alcohol use such as the Alcohol Use Disorders Identification Test (AUDIT) and its shortened form (AUDIT-C), but there remains significant variation across studies, and validated measures simply do not exist for some outcomes.

Most of the studies were conducted in clinic-based or through convenience samples, which suffer from selection bias.<sup>28</sup> Specifically, studies that aimed to assess behavior change after diagnosis among a sample of HIV care attending patients will necessarily exclude out-of-care populations who likely have lower health-seeking tendencies. Some studies also had strict exclusion criteria and/or high rates of non-participation, which would likely result in similar biases. In addition, most studies were conducted in resource-rich, predominantly urban settings, and therefore may not be generalizable to other populations due to differences in demographic compositions and

contextual risk factors.<sup>113</sup> For example, several recent studies in the Multicenter AIDS Cohort Study and Women's Interagency HIV Study (in the US and Europe) have found that risk behavior engagement is strongly predicted by race/ethnicity, economic stability and societal/peer norms, concepts that would likely differ in meaning and importance in other cultures.<sup>38, 114-116</sup> Thus, further research in other settings is essential for developing region-specific knowledge and interventions. Last, some studies were specifically targeted towards high HIV-risk populations (e.g., MSM, drug users or female sex workers) and their results would not be applicable to the general population.

#### ***2.4.1. Strengths and limitations***

Our study has several key strengths and limitations. This is the first study to our knowledge to review the evidence of the effects of HIV on CVD risk behaviors.<sup>32, 117</sup> We improved on the existing literature by explicitly disaggregating analyses by HIV continuum stage to examine patterns across stage. We also considered multiple CVD risk behaviors, hypothesizing that relationships would be similar across all CVD risk behaviors. Our review showed that findings were generally consistent between smoking and alcohol use, and that minimal research attention has been placed on dietary and sedentary behaviors to date. An important limitation is that in the process of stratifying our analysis by HIV continuum stage, the sample size of available studies was reduced for each comparison of interest. We expanded the review to include cross-sectional studies that were not designed specifically to examine the relationship between HIV and CVD risk behaviors; we expect that this would have broad impacts on each study's target population, variable measurements and analytical choices, contributing to the disparate findings we observed. In addition, we excluded studies where the direction of causation was known to be in the opposite direction. As a result, studies that were unable to establish temporality were more

likely to be retained in the analysis, which may have introduced bias in the selection of studies for our review.

## **2.5. Conclusion**

Overall, our review provides modest support for causal effects of HIV infection and awareness and protective effects of HIV treatment and recovery on CVD risk behaviors, with the strongest and most consistent findings found for smoking compared to other CVD risk behaviors. Our findings suggest that the relationships differ by HIV continuum stage, though few studies operationalize HIV continuum stage adequately to answer this question. These findings have implications for clinical practice, as most individuals with HIV are diagnosed at advanced stages of HIV. Our review supports recent research suggesting that receiving an HIV diagnosis may indeed be a teachable moment, though evidence from intervention studies would be required to confirm whether efforts to translate intention to actual behavior change are effective and can be maintained over time.<sup>62</sup> Future research is also required to ascertain the underlying mechanisms of the relationship, including directly testing whether stress explains the observed associations.

## 2.6. References

1. Sackoff, J.E., D.B. Hanna, M.R. Pfeiffer, et al., *Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City*. Ann Intern Med, 2006. **145**(6): p. 397-406.
2. Glass, T.R., C. Ungsedhapand, M. Wolbers, et al., *Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study*. HIV Med, 2006. **7**(6): p. 404-10.
3. Tesoriero, J.M., S.M. Gieryic, A. Carrascal, et al., *Smoking among HIV positive New Yorkers: prevalence, frequency, and opportunities for cessation*. AIDS Behav, 2010. **14**(4): p. 824-35.
4. Lifson, A.R. and H.A. Lando, *Smoking and HIV: prevalence, health risks, and cessation strategies*. Curr HIV/AIDS Rep, 2012. **9**(3): p. 223-30.
5. Mdodo, R., E.L. Frazier, S.R. Dube, et al., *Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys*. Ann Intern Med, 2015. **162**(5): p. 335-44.
6. Weinberger, A.H., P.H. Smith, A.P. Funk, et al., *Sex Differences in Tobacco Use Among Persons Living With HIV/AIDS: A Systematic Review and Meta-Analysis*. J Acquir Immune Defic Syndr., 2017. **74**(4): p. 439-453. doi: 10.1097/QAI.0000000000001279.
7. Shiau, S., S.M. Arpadi, M.T. Yin, et al., *Patterns of drug use and HIV infection among adults in a nationally representative sample*. Addict Behav., 2017. **68**:39-44.(doi): p. 10.1016/j.addbeh.2017.01.015. Epub 2017 Jan 7.
8. Mdege, N.D., S. Shah, O.A. Ayo-Yusuf, et al., *Tobacco use among people living with HIV: analysis of data from Demographic and Health Surveys from 28 low-income and middle-income countries*. Lancet Glob Health., 2017. **5**(6): p. e578-e592. doi: 10.1016/S2214-109X(17)30170-5.
9. Gritz, E.R., D.J. Vidrine, A.B. Lazev, et al., *Smoking behavior in a low-income multiethnic HIV/AIDS population*. Nicotine Tob Res., 2004. **6**(1): p. 71-7.
10. Crane, H.M., M.E. McCaul, G. Chander, et al., *Prevalence and Factors Associated with Hazardous Alcohol Use Among Persons Living with HIV Across the US in the Current Era of Antiretroviral Treatment*. AIDS Behav, 2017. **11**(10): p. 017-1740.
11. Ikeda, M.L., N.T. Barcellos, P.R. Alencastro, et al., *Alcohol Drinking Pattern: A Comparison between HIV-Infected Patients and Individuals from the General*

- Population*. PLoS One., 2016. **11**(6): p. e0158535. doi: 10.1371/journal.pone.0158535. eCollection 2016.
12. Fisher, J.C., H. Bang, and S.H. Kapiga, *The association between HIV infection and alcohol use: a systematic review and meta-analysis of African studies*. Sex Transm Dis, 2007. **34**(11): p. 856-63.
  13. Galvan, F.H., E.G. Bing, J.A. Fleishman, et al., *The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study*. J Stud Alcohol., 2002. **63**(2): p. 179-86.
  14. Kelso, N.E., D.S. Sheps, and R.L. Cook, *The association between alcohol use and cardiovascular disease among people living with HIV: a systematic review*. Am J Drug Alcohol Abuse, 2015. **41**(6): p. 479-88.
  15. Joy, T., H.M. Keogh, C. Hadigan, et al., *Dietary fat intake and relationship to serum lipid levels in HIV-infected patients with metabolic abnormalities in the HAART era*. AIDS., 2007. **21**(12): p. 1591-600. doi: 10.1097/QAD.0b013e32823644ff.
  16. Schafer, J., J. Young, A. Calmy, et al., *High prevalence of physical inactivity among patients from the Swiss HIV Cohort Study*. AIDS Care., 2017. **29**(8): p. 1056-1061. doi: 10.1080/09540121.2016.1274016. Epub 2017 Jan 5.
  17. Schuelter-Trevisol, F., F.H. Wolff, P.R. Alencastro, et al., *Physical activity: do patients infected with HIV practice? How much? A systematic review*. Curr HIV Res., 2012. **10**(6): p. 487-97.
  18. Schneider, M., M. Chersich, M. Temmerman, et al., *The impact of alcohol on HIV prevention and treatment for South Africans in primary healthcare*. Curationis., 2014. **37**(1): p. 1137. doi: 10.4102/curationis.v37i1.1137.
  19. Shuter, J. and S.L. Bernstein, *Cigarette smoking is an independent predictor of nonadherence in HIV-infected individuals receiving highly active antiretroviral therapy*. Nicotine Tob Res, 2008. **10**(4): p. 731-6.
  20. Conserve, D., G. King, A. Turo, et al., *Cigarette smoking and alcohol use as predictors of HIV testing in the United States: results from the 2010 National Health Interview Survey*. AIDS Care, 2014. **26**(7): p. 842-9.
  21. Marshall, M.M., M.C. McCormack, and G.D. Kirk, *Effect of cigarette smoking on HIV acquisition, progression, and mortality*. AIDS Educ Prev., 2009. **21**(3 Suppl): p. 28-39. doi: 10.1521/aeap.2009.21.3\_supp.28.

22. Shuper, P.A., M. Neuman, F. Kanteres, et al., *Causal considerations on alcohol and HIV/AIDS--a systematic review*. Alcohol Alcohol., 2010. **45**(2): p. 159-66. doi: 10.1093/alcalc/agg091. Epub 2010 Jan 8.
23. Nicholas, P.K., J.G. Voss, I.B. Corless, et al., *Unhealthy behaviours for self-management of HIV-related peripheral neuropathy*. AIDS Care., 2007. **19**(10): p. 1266-73.
24. Rod, N.H., M. Gronbaek, P. Schnohr, et al., *Perceived stress as a risk factor for changes in health behaviour and cardiac risk profile: a longitudinal study*. J Intern Med., 2009. **266**(5): p. 467-75. doi: 10.1111/j.1365-2796.2009.02124.x. Epub 2009 Apr 23.
25. Browning, K.K., M.E. Wewers, A.K. Ferketich, et al., *Tobacco use and cessation in HIV-infected individuals*. Clin Chest Med, 2013. **34**(2): p. 181-90.
26. Fuster, M., V. Estrada, M.C. Fernandez-Pinilla, et al., *Smoking cessation in HIV patients: rate of success and associated factors*. HIV Med, 2009. **10**(10): p. 614-9.
27. Elliott, J.C., E. Aharonovich, and D.S. Hasin, *Reasons for limiting drinking in an HIV primary care sample*. Alcohol Clin Exp Res, 2014. **38**(6): p. 1720-7.
28. Wong, C., K. Althoff, and S.J. Gange, *Identifying the appropriate comparison group for HIV-infected individuals*. Curr Opin HIV AIDS, 2014. **9**(4): p. 379-85.
29. Tsui, J.I., D.M. Cheng, S.M. Coleman, et al., *Pain and Risk Behaviors Among HIV-Infected Persons in St. Petersburg, Russia*. AIDS Behav., 2017. **21**(6): p. 1775-1781. doi: 10.1007/s10461-016-1593-5.
30. Weinberger, A.H., E.K. Seng, J.W. Ditte, et al., *Perceived interrelations of pain and cigarette smoking in a sample of adult smokers living with HIV/AIDS*. Nicotine Tob Res, 2018. **31**(4830708).
31. Regan, S., J.B. Meigs, S.K. Grinspoon, et al., *Determinants of Smoking and Quitting in HIV-Infected Individuals*. PLoS One., 2016. **11**(4): p. e0153103. doi: 10.1371/journal.pone.0153103. eCollection 2016.
32. Reynolds, N.R., *Cigarette smoking and HIV: more evidence for action*. AIDS Educ Prev., 2009. **21**(3 Suppl): p. 106-21. doi: 10.1521/aeap.2009.21.3\_supp.106.
33. Elliott, J.C., E. Aharonovich, A. O'Leary, et al., *Drinking motives among HIV primary care patients*. AIDS Behav., 2014. **18**(7): p. 1315-23. doi: 10.1007/s10461-013-0644-4.

34. Webb, M.S., P.A. Vanable, M.P. Carey, et al., *Cigarette smoking among HIV+ men and women: examining health, substance use, and psychosocial correlates across the smoking spectrum*. J Behav Med., 2007. **30**(5): p. 371-83. Epub 2007 Jun 15.
35. Wang, Y., X. Chen, J. Ball, et al., *Self-reported changes in alcohol use behavior among people living with HIV in China after receiving HIV positive diagnosis*. SAGE Open Med., 2018. **6**:2050312118755783.(doi): p. 10.1177/2050312118755783. eCollection 2018.
36. Wang, Y., X. Chen, X. Li, et al., *Cigarette smoking among Chinese PLWHA: An exploration of changes in smoking after being tested HIV positive*. AIDS Care, 2016. **28**(3): p. 365-9.
37. Feinstein, M.J., J.H. Kim, P. Bibangambah, et al., *Ideal Cardiovascular Health and Carotid Atherosclerosis in a Mixed Cohort of HIV-Infected and Uninfected Ugandans*. AIDS Res Hum Retroviruses, 2017. **33**(1): p. 49-56.
38. Akhtar-Khaleel, W.Z., R.L. Cook, S. Shoptaw, et al., *Trends and Predictors of Cigarette Smoking Among HIV Seropositive and Seronegative Men: The Multicenter Aids Cohort Study*. AIDS Behav., 2016. **20**(3): p. 622-32. doi: 10.1007/s10461-015-1099-6.
39. Aralis, H.J., S. Shoptaw, R. Brookmeyer, et al., *Psychiatric Illness, Substance Use, and Viral Suppression Among HIV-Positive Men of Color Who Have Sex with Men in Los Angeles*. AIDS Behav, 2018. **24**(10): p. 018-2055.
40. Baker, J.V., S. Sharma, A.C. Achhra, et al., *Changes in Cardiovascular Disease Risk Factors With Immediate Versus Deferred Antiretroviral Therapy Initiation Among HIV-Positive Participants in the START (Strategic Timing of Antiretroviral Treatment) Trial*. J Am Heart Assoc, 2017. **6**(5).
41. Bekele, T., S. Rueda, S. Gardner, et al., *Trends and Correlates of Cigarette Smoking and Its Impacts on Health-Related Quality of Life Among People Living with HIV: Findings from the Ontario HIV Treatment Network Cohort Study, 2008-2014*. AIDS Patient Care STDS, 2017. **31**(2): p. 49-59.
42. Benard, A., J.F. Tessier, J. Rambeloarisoa, et al., *HIV infection and tobacco smoking behaviour: prospects for prevention? ANRS CO3 Aquitaine Cohort, 2002*. Int J Tuberc Lung Dis, 2006. **10**(4): p. 378-83.
43. Bergersen, B.M., L. Sandvik, J.N. Bruun, et al., *Elevated Framingham risk score in HIV-positive patients on highly active antiretroviral therapy: results from a Norwegian study of 721 subjects*. Eur J Clin Microbiol Infect Dis, 2004. **23**(8): p. 625-30.

44. Brath, H., I. Grabovac, H. Schalk, et al., *Prevalence and Correlates of Smoking and Readiness to Quit Smoking in People Living with HIV in Austria and Germany*. PLoS One, 2016. **11**(2): p. e0150553.
45. Brown, J.L., T. Winhusen, R.J. DiClemente, et al., *The association between cigarette smoking, virologic suppression, and CD4+ lymphocyte count in HIV-Infected Russian women*. AIDS Care., 2017. **29**(9): p. 1102-1106. doi: 10.1080/09540121.2017.1327645. Epub 2017 May 12.
46. Burkhalter, J.E., C.M. Springer, R. Chhabra, et al., *Tobacco use and readiness to quit smoking in low-income HIV-infected persons*. Nicotine Tob Res., 2005. **7**(4): p. 511-22.
47. Collins, R.L., D.E. Kanouse, A.L. Gifford, et al., *Changes in health-promoting behavior following diagnosis with HIV: prevalence and correlates in a national probability sample*. Health Psychol., 2001. **20**(5): p. 351-60.
48. De Socio, G.V., L. Martinelli, S. Morosi, et al., *Is estimated cardiovascular risk higher in HIV-infected patients than in the general population?* Scand J Infect Dis, 2007. **39**(9): p. 805-12.
49. Duval, X., G. Baron, D. Garelik, et al., *Living with HIV, antiretroviral treatment experience and tobacco smoking: results from a multisite cross-sectional study*. Antivir Ther, 2008. **13**(3): p. 389-97.
50. Elf, J.L., E. Variava, S. Chon, et al., *Prevalence and Correlates of Smoking Among People Living With HIV in South Africa*. Nicotine Tob Res, 2017. **21**(3883619).
51. Etukumana, E.A., T.D. Thacher, and A.S. Sagay, *HIV risk factors among pregnant women in a rural Nigerian hospital*. West Indian Med J, 2010. **59**(4): p. 424-8.
52. Gutierrez, J., M.S. Elkind, and R.S. Marshall, *Cardiovascular profile and events of US adults 20-49 years with HIV: results from the NHANES 1999-2008*. AIDS Care, 2013. **25**(11): p. 1385-91.
53. Hanna, D.B., M. Jung, X. Xue, et al., *Trends in Nonlipid Cardiovascular Disease Risk Factor Management in the Women's Interagency HIV Study and Association with Adherence to Antiretroviral Therapy*. AIDS Patient Care STDS., 2016. **30**(10): p. 445-454.
54. Jaquet, A., D.K. Ekouevi, M. Aboubakrine, et al., *Tobacco use and its determinants in HIV-infected patients on antiretroviral therapy in West African countries*. International Journal of Tuberculosis and Lung Disease, 2009. **13**(11): p. 1433-1439.

55. Luo, X., S. Duan, Q. Duan, et al., *Tobacco use among HIV-infected individuals in a rural community in Yunnan Province, China*. *Drug and Dependence*, 2014. **134**(1): p. 144-150.
56. Oka, F., T. Naito, M. Oike, et al., *Influence of smoking on HIV infection among HIV-infected Japanese men*. *J Infect Chemother*, 2013. **19**(3): p. 542-4.
57. Petoumenos, K., R. Huang, J. Hoy, et al., *Prevalence of self-reported comorbidities in HIV positive and HIV negative men who have sex with men over 55 years-The Australian Positive & Peers Longevity Evaluation Study (APPLES)*. *Plos One*, 2017. **12**(9).
58. Pollack, T.M., H.T. Duong, T.T. Pham, et al., *Cigarette smoking is associated with high HIV viral load among adults presenting for antiretroviral therapy in Vietnam*. *PLoS One*, 2017. **12**(3): p. e0173534. doi: 10.1371/journal.pone.0173534. eCollection 2017.
59. Shariati, H., H.L. Armstrong, Z. Cui, et al., *Changes in smoking status among a longitudinal cohort of gay, bisexual, and other men who have sex with men in Vancouver, Canada*. *Drug Alcohol Depend.*, 2017. **179:370-378**.(doi): p. 10.1016/j.drugalcdep.2017.07.025. Epub 2017 Aug 16.
60. Shokoohi, M., G.R. Bauer, A. Kaida, et al., *Substance use patterns among women living with HIV compared with the general female population of Canada*. *Drug and Alcohol Dependence*, 2018. **191**: p. 70-77.
61. Tron, L., F. Lert, B. Spire, et al., *Tobacco smoking in HIV-infected versus general population in France: Heterogeneity across the various groups of people living with HIV*. *PLoS ONE*, 2014. **9**(9).
62. Vidrine, D.J., S.G. Frank, M.J. Savin, et al., *HIV Care Initiation: A Teachable Moment for Smoking Cessation?* *Nicotine Tob Res.*, 2018. **20**(9): p. 1109-1116. doi: 10.1093/ntr/ntx218.
63. Zyambo, C.M., J.H. Willig, K.L. Cropsey, et al., *Factors Associated With Smoking Status among HIV-Positive Patients in Routine Clinical Care*. *J AIDS Clin Res.*, 2015. **6**(7).(pii): p. 480. Epub 2015 Jul 9.
64. Allen, C.F., Y. Simon, J. Edwards, et al., *Adherence to antiretroviral therapy by people accessing services from non-governmental HIV support organisations in three Caribbean countries*. *West Indian Med J*, 2011. **60**(3): p. 269-75.
65. Applebaum, A.J., M.A. Richardson, S.M. Brady, et al., *Gender and other psychosocial factors as predictors of adherence to highly active antiretroviral therapy (HAART) in adults with comorbid HIV/AIDS, psychiatric and substance-related disorder*. *AIDS Behav*, 2009. **13**(1): p. 60-5.

66. Arnsten, J.H., P.A. Demas, R.W. Grant, et al., *Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users*. J Gen Intern Med, 2002. **17**(5): p. 377-81.
67. Bilal, U., M.E. McCaul, H.M. Crane, et al., *Predictors of Longitudinal Trajectories of Alcohol Consumption in People with HIV*. Alcohol Clin Exp Res., 2018. **42**(3): p. 561-570. doi: 10.1111/acer.13583. Epub 2018 Jan 29.
68. Chander, G., J. Josephs, J.A. Fleishman, et al., *Alcohol use among HIV-infected persons in care: Results of a multi-site survey*. HIV Medicine, 2008. **9**(4): p. 196-202.
69. Chersich, M.F., S.M. Luchters, I.M. Malonza, et al., *Heavy episodic drinking among Kenyan female sex workers is associated with unsafe sex, sexual violence and sexually transmitted infections*. Int J STD AIDS, 2007. **18**(11): p. 764-9.
70. Cook, R.L., Z. Zhou, N.E. Kelso-Chichetto, et al., *Alcohol consumption patterns and HIV viral suppression among persons receiving HIV care in Florida: an observational study*. Addict Sci Clin Pract., 2017. **12**(1): p. 22. doi: 10.1186/s13722-017-0090-0.
71. Cook, R.L., F. Zhu, B.H. Belnap, et al., *Alcohol consumption trajectory patterns in adult women with HIV infection*. AIDS Behav, 2013. **17**(5): p. 1705-12.
72. da Silva, C.M., R.A. Mendoza-Sassi, L.D. da Mota, et al., *Alcohol use disorders among people living with HIV/AIDS in Southern Brazil: prevalence, risk factors and biological markers outcomes*. BMC Infect Dis., 2017. **17**(1): p. 263. doi: 10.1186/s12879-017-2374-0.
73. Do, H.M., M.P. Dunne, M. Kato, et al., *Factors associated with suboptimal adherence to antiretroviral therapy in Viet Nam: a cross-sectional study using audio computer-assisted self-interview (ACASI)*. BMC Infect Dis, 2013. **13**: p. 154.
74. Du Bois, S.N. and D.J. McKirnan, *A longitudinal analysis of HIV treatment adherence among men who have sex with men: A cognitive escape perspective*. Aids Care- Psychological and Socio-Medical Aspects of Aids/Hiv, 2012. **24**(11): p. 1425-1431.
75. Elliott, J.C., E. Delker, M.M. Wall, et al., *Neighborhood-Level Drinking Norms and Alcohol Intervention Outcomes in HIV Patients Who Are Heavy Drinkers*. Alcohol Clin Exp Res, 2016. **40**(10): p. 2240-2246.
76. Elul, B., P. Basinga, H. Nuwagaba-Biribonwoha, et al., *High levels of adherence and viral suppression in a nationally representative sample of HIV-infected adults on antiretroviral therapy for 6, 12 and 18 months in Rwanda*. PLoS One, 2013. **8**(1): p. e53586.

77. Ferro, E.G., D. Weikum, P. Vagenas, et al., *Alcohol use disorders negatively influence antiretroviral medication adherence among men who have sex with men in Peru*. *AIDS Care*, 2015. **27**(1): p. 93-104. doi: 10.1080/09540121.2014.963013. Epub 2014 Oct 3.
78. Ghebremichael, M. and E. Paintsil, *High risk behaviors and sexually transmitted infections among men in Tanzania*. *AIDS Behav*, 2011. **15**(5): p. 1026-32.
79. Goulet, J.L., S.L. Fultz, D. Rimland, et al., *Do patterns of comorbidity vary by HIV status, age, and HIV severity?* *Clinical Infectious Diseases*, 2007. **45**(12): p. 1593-1601.
80. Grierson, J., R.L. Koelmeyer, A. Smith, et al., *Adherence to antiretroviral therapy: factors independently associated with reported difficulty taking antiretroviral therapy in a national sample of HIV-positive Australians*. *HIV Med*, 2011. **12**(9): p. 562-9.
81. Inciardi, J.A., H.L. Surratt, S.P. Kurtz, et al., *The effect of serostatus on HIV risk behaviour change among women sex workers in Miami, Florida*. *AIDS Care*, 2005. **17 Suppl 1**: p. S88-101.
82. Jaquet, A., D.K. Ekouevi, J. Bashi, et al., *Alcohol use and non-adherence to antiretroviral therapy in HIV-infected patients in West Africa*. *Addiction*, 2010. **105**(8): p. 1416-21.
83. Kelso-Chichetto, N.E., M. Plankey, A.G. Abraham, et al., *Association between alcohol consumption trajectories and clinical profiles among women and men living with HIV*. *Am J Drug Alcohol Abuse*, 2017. **16**: p. 1-10.
84. Kunzweiler, C.P., R.C. Bailey, D.O. Okall, et al., *Factors Associated With Prevalent HIV Infection Among Kenyan MSM: The Anza Mapema Study*. *J Acquir Immune Defic Syndr.*, 2017. **76**(3): p. 241-249. doi: 10.1097/QAI.0000000000001512.
85. Lancaster, K.E., V.F. Go, T. Lungu, et al., *Substance use and HIV infection awareness among HIV-infected female sex workers in Lilongwe, Malawi*. *Int J Drug Policy*, 2016. **30**: p. 124-31.
86. Lancaster, K.E., T. Lungu, P. Mmodzi, et al., *The association between substance use and sub-optimal HIV treatment engagement among HIV-infected female sex workers in Lilongwe, Malawi*. *AIDS Care*, 2017. **29**(2): p. 197-203.
87. Magidson, J.F., W. Saal, A. Nel, et al., *Relationship between depressive symptoms, alcohol use, and antiretroviral therapy adherence among HIV-infected, clinic-attending patients in South Africa*. *J Health Psychol.*, 2017. **22**(11): p. 1426-1433. doi: 10.1177/1359105316628743. Epub 2016 Feb 15.

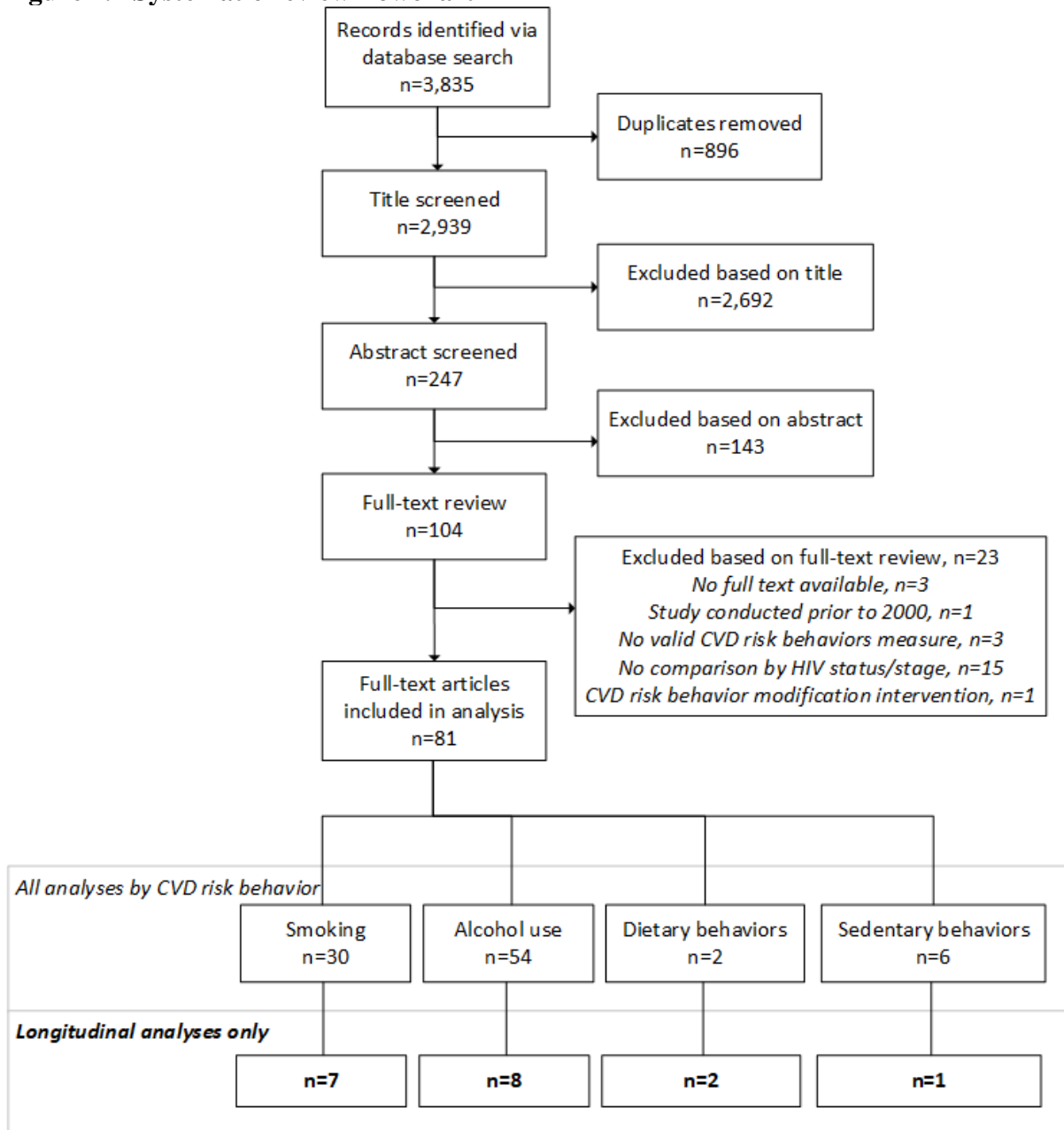
88. Marshall, B.D.L., J.P. Tate, K.A. McGinnis, et al., *Long-term alcohol use patterns and HIV disease severity*. *AIDS.*, 2017. **31**(9): p. 1313-1321. doi: 10.1097/QAD.0000000000001473.
89. Martinez, P., I. Andia, N. Emenyonu, et al., *Alcohol use, depressive symptoms and the receipt of antiretroviral therapy in southwest Uganda*. *AIDS Behav.*, 2008. **12**(4): p. 605-12. Epub 2007 Oct 30.
90. Medley, A., P. Seth, S. Pathak, et al., *Alcohol use and its association with HIV risk behaviors among a cohort of patients attending HIV clinical care in Tanzania, Kenya, and Namibia*. *AIDS Care*, 2014. **26**(10): p. 1288-97.
91. Monroe, A.K., B. Lau, M.J. Mugavero, et al., *Heavy Alcohol Use Is Associated With Worse Retention in HIV Care*. *J Acquir Immune Defic Syndr*, 2016. **73**(4): p. 419-425.
92. Msuya, S.E., E. Mbizvo, A. Hussain, et al., *HIV among pregnant women in Moshi Tanzania: the role of sexual behavior, male partner characteristics and sexually transmitted infections*. *AIDS Res Ther*, 2006. **3**: p. 27.
93. Nuken, A., M. Kermode, N. Saggurti, et al., *Alcohol and condom use among HIV-positive and HIV-negative female sex workers in Nagaland, India*. *Int J STD AIDS*, 2013. **24**(9): p. 695-702.
94. Pecoraro, A., M. Mimiaga, C. O'Cleirigh, et al., *Depression, substance use, viral load, and CD4+ count among patients who continued or left antiretroviral therapy for HIV in St. Petersburg, Russian Federation*. *AIDS Care*, 2015. **27**(1): p. 86-92.
95. Probst, C., L.C. Simbayi, C.D.H. Parry, et al., *Alcohol Use, Socioeconomic Status and Risk of HIV Infections*. *AIDS Behav*, 2017. **21**(7): p. 1926-1937.
96. Ramlagan, S., K. Peltzer, R.A.C. Ruiters, et al., *Prevalence and Factors Associated with Fixed-Dose Combination Antiretroviral Drugs Adherence among HIV-Positive Pregnant Women on Option B Treatment in Mpumalanga Province, South Africa*. *Int J Environ Res Public Health.*, 2018. **15**(1).(pii): p. ijerph15010161. doi: 10.3390/ijerph15010161.
97. Sacamano, P.L. and J.E. Farley, *Behavioral and Other Characteristics Associated with HIV Viral Load in an Outpatient Clinic*. *Plos One*, 2016. **11**(11).
98. Sarna, A., W. Tun, V. Sharma, et al., *High uptake of HIV testing in a cohort of male injection drug users in Delhi, India: prevalence and correlates of HIV infection*. *AIDS Behav*, 2013. **17**(7): p. 2479-89.

99. Scott-Sheldon, L.A., M.P. Carey, K.B. Carey, et al., *Does perceived life stress mediate the association between HIV status and alcohol use? Evidence from adults living in Cape Town, South Africa*. *AIDS Care.*, 2013. **25**(8): p. 1026-32. doi: 10.1080/09540121.2012.749335. Epub 2013 Jan 18.
100. Sebit, M.B., M. Tombe, S. Siziya, et al., *Prevalence of HIV/AIDS and psychiatric disorders and their related risk factors among adults in Epworth, Zimbabwe*. *East Afr Med J*, 2003. **80**(10): p. 503-12.
101. Shaffer, D.N., R. Njeri, A.C. Justice, et al., *Alcohol abuse among patients with and without HIV infection attending public clinics in western Kenya*. *East Afr Med J*, 2004. **81**(11): p. 594-8.
102. Sullivan, L.E., J.L. Goulet, A.C. Justice, et al., *Alcohol consumption and depressive symptoms over time: a longitudinal study of patients with and without HIV infection*. *Drug Alcohol Depend*, 2011. **117**(2-3): p. 158-63.
103. Tran, B.X., N. Nguyen, A. Ohinmaa, et al., *Prevalence and correlates of alcohol use disorders during antiretroviral treatment in injection-driven HIV epidemics in Vietnam*. *Drug Alcohol Depend*, 2013. **127**(1-3): p. 39-44.
104. Vagenas, P., K.T. Ludford, P. Gonzales, et al., *Being unaware of being HIV-infected is associated with alcohol use disorders and high-risk sexual behaviors among men who have sex with men in Peru*. *AIDS Behav*, 2014. **18**(1): p. 120-7.
105. Veld, D.H.I., S. Pengpid, R. Colebunders, et al., *High-risk alcohol use and associated socio-demographic, health and psychosocial factors in patients with HIV infection in three primary health care clinics in South Africa*. *Int J STD AIDS*, 2017. **28**(7): p. 651-659.
106. Wandera, B., N.M. Tumwesigye, J.I. Nankabirwa, et al., *Alcohol consumption among HIV-infected persons in a large urban HIV clinic in Kampala Uganda: A constellation of harmful behaviors*. *PLoS ONE*, 2015. **10**(5).
107. Yaya, I., D.E. Landoh, B. Saka, et al., *Predictors of adherence to antiretroviral therapy among people living with HIV and AIDS at the regional hospital of Sokode, Togo*. *BMC Public Health*, 2014. **14**: p. 1308.
108. Jacob, T., D.M. Blonigen, R. Upah, et al., *Lifetime drinking trajectories among veterans in treatment for HIV*. *Alcohol Clin Exp Res.*, 2013. **37**(7): p. 1179-87. doi: 10.1111/acer.12071. Epub 2013 Feb 28.

109. Hendricks, K.M., D.M. Mwamburi, P.K. Newby, et al., *Dietary patterns and health and nutrition outcomes in men living with HIV infection*. Am J Clin Nutr, 2008. **88**(6): p. 1584-92.
110. Silveira, E.A., A. Santos, M.O. Falco, et al., *Association of physical inactivity with hypertension and low educational level in people living with HIV / AIDS*. AIDS Care, 2018. **22**: p. 1-6.
111. Stein, L., D. Hechler, A.B. Jessen, et al., *Sports behaviour among HIV-infected versus non-infected individuals in a Berlin cohort*. Int J STD AIDS, 2012. **23**(1): p. 25-9.
112. Vidrine, D.J., G. Kypriotakis, L. Li, et al., *Mediators of a smoking cessation intervention for persons living with HIV/AIDS*. Drug Alcohol Depend., 2015. **147**:76-80.(doi): p. 10.1016/j.drugalcdep.2014.12.003. Epub 2014 Dec 15.
113. Petersen, M., C.T. Yiannoutsos, A. Justice, et al., *Observational research on NCDs in HIV-positive populations: conceptual and methodological considerations*. J Acquir Immune Defic Syndr, 2014. **67 Suppl 1**: p. S8-16.
114. Boodram, B., M.W. Plankey, C. Cox, et al., *Prevalence and correlates of elevated body mass index among HIV-positive and HIV-negative women in the Women's Interagency HIV Study*. AIDS Patient Care STDS., 2009. **23**(12): p. 1009-16. doi: 10.1089/apc.2009.0175.
115. Cook, R.L., C.L. Cook, M. Karki, et al., *Perceived benefits and negative consequences of alcohol consumption in women living with HIV: a qualitative study*. BMC Public Health., 2016. **16**:263.(doi): p. 10.1186/s12889-016-2928-x.
116. Goldberg, D., K.M. Weber, J. Orsi, et al., *Smoking cessation among women with and at risk for HIV: are they quitting?* J Gen Intern Med., 2010. **25**(1): p. 39-44. doi: 10.1007/s11606-009-1150-2. Epub 2009 Nov 17.
117. Browning, K.K., M.E. Wewers, A.K. Ferketich, et al., *The Self-regulation Model of Illness applied to smoking behavior in lung cancer*. Cancer Nurs., 2009. **32**(4): p. E15-25. doi: 10.1097/NCC.0b013e3181a0238f.

## 2.7. Figures and Tables

**Figure 2.1 Systematic review flowchart**



Note: Sum of analyses by CVD risk behavior exceeds number of articles in full text review since some articles reported on multiple CVD risk behaviors.

**Table 2.1 Longitudinal analyses of smoking change by HIV continuum stage**

No.	Author(s) (year)	Location	Population (n)	Sampling	Smoking measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
1	Akhtar-Khaleel et al. (2016)	United States	HIV+ and HIV-MSM (n=6,577)	Clinic-based (Multicenter AIDS Cohort Study)	Smoking trajectory (self-report: current smoking at multiple visits)	HIV status (blood test)	Persistent heavy smoking vs. non-smoking among HIV+ vs. HIV-	adjusted PR = 1.17 (1.01, 1.34)	race, education, enrollment date, employment, alcohol use, marijuana use, hospitalizations, depression
						ART use (self-report: combined therapy)	Persistent heavy smoking vs. non-smoking among ART users vs. non-users	growth parameter* = 0.0059 (p-value = NS)	
						VL detectable (blood test)	Persistent heavy smoking vs. non-smoking among undetectable vs. detectable VL <sup>†</sup>	growth parameter* < -0.0001 (p-value = NS)	
2	Baker et al. (2017)	United States	HIV+ persons (n=4685)	Nested within RCT of ART initiation strategies	Smoking (self-report)	Deferred HIV treatment initiation (treat at CD4 <500 vs immediate)	Smoking among immediate vs. deferred HIV treatment initiation	$\beta = -0.2$ (-2.2, 1.7)	baseline prevalence and visit
3	Collins et al. (2001)	United States	HIV+ persons in care (n=2,864)	Clinic-based, probability sample	Smoking (self-report)	HIV diagnosis (self-report)	Change in smoking after HIV diagnosis	prevalence of reduced smoking = 49%	age, gender, ethnicity, marital status, education, drug use, CD4, symptom, self-rated health, physical functioning, stress and coping
4	Hanna et al. (2016)	United States	HIV+ (n=806) and HIV- (n=400) women smokers	Clinic-based	Quit smoking since last visit (self-report)	HIV serostatus (blood test)	Quit smoking since last visit among HIV+ vs. HIV-	prevalence = 10% vs. 9%; (p-value=0.33)	unadjusted
5	Shariati et al. (2017)	Vancouver, Canada	16yo+ gay or bisexual MSM (n=525)	Respondent-driven sampling	Daily smoking (self-report)	HIV status (blood test: HIV+, HIV-, unknown status)	Daily smoking among HIV+ vs. HIV- vs. unknown	prevalence = 33.1% vs. 28.8% vs. 45.3%; (p=0.004)	income, current self-rated health, partner tobacco use, drinking type, ecstasy use
					Smoking cessation (self-report)		Smoking cessation among HIV+ vs. HIV-	unadjusted mixed model RR = 2.10 (0.87, 1.75)	
6	Vidrine et al. (2018)	Houston, United States	HIV+ persons who currently smoke and are initiating HIV care (n=378)	Clinic-based	Smoking (biomarker: expired CO)	Time since HIV care initiation (medical visit attendance records)	Smoking trends over time since HIV care initiation	prevalence every 3 months after HIV care initiation = 10%, 12%, 14%, 8%	age, gender identity, race/ethnicity, education, work status, route of HIV transmission, drug/alcohol use, depressive symptoms, affect, social support, nicotine dependence

No.	Author(s) (year)	Location	Population (n)	Sampling	Smoking measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
7	Wang et al. (2016)	Guangxi, China	HIV+ persons (n=2964)	Population-based (PLWH census)	Change in smoking after HIV diagnosis (self-report: increased vs. reduced vs. quit)	HIV diagnosis (self- report)	Change in smoking after HIV diagnosis	prevalence = 28.9% reduced, 19.0% quit, 8.2% relapsed/increased	unadjusted

Note: † denotes relationships that were transformed from the original publication to facilitate comparison across studies.

\* growth-specific parameters from group-based trajectory model

Abbreviations: AACTG: Adult AIDS Clinical Trials Group, AIDS: Acquired Immune Deficiency Syndrome, ANC: Antenatal care, ART: Antiretroviral therapy, BMI: Body mass index, CO: Carbon monoxide, CVD: Cardiovascular disease, FSW: Female sex workers, HIV: Human immunodeficiency virus, IDU: Injection drug users, IeDEA: International Epidemiology Databases to Evaluate AIDS, MACS: Multicenter AIDS Cohort Study, MSM: Men who have sex with men, NHIS: National Health Interview Survey, OR: Odds ratio, PR: Prevalence ratio, RR: Risk ratio, SA NHANES: South Africa National Health and Nutrition Examination Survey, TB: Tuberculosis, VACS: Veterans Aging Cohort Study, VAS: Visual Analog Scale, VL: Viral load, VLS: Viral load suppression, WHO: World Health Organization, WIHS: Women's Interagency HIV Study

**Table 2.2 Longitudinal analyses of alcohol use change by HIV continuum stage**

No.	Author(s) (year)	Location	Population (n)	Sampling	Alcohol measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
1	Arnsten et al. (2002)	Bronx, United States	HIV+ current and former drug users in care (n=85)	Clinic-based	Frequent alcohol use, past 6 months (self-report)	ART adherence 0- 100%, past 6 months (MEMS)	ART adherence among frequent vs. non-frequent alcohol use trajectories	Mean adherence = 37% vs. 62% (Kruskal Wallis p=0.09)	not stated, possibly includes demographics, socioeconomic variables, HIV health, drug use
						VLS (blood test)	VLS among frequent vs. non-frequent alcohol use trajectories	Mean adherence = 21% vs. 41% (Kruskal Wallis p=0.1)	
2	Bilal et al. (2018)	United States	HIV+ patients in care in CNICS clinics (n=7906)	Clinic-based	Started alcohol use, past 3 years (self- report)	Baseline VLS (blood test)	Started alcohol use trajectory among VLS vs. not VLS at baseline	adjusted multinomial OR = 0.9 (0.7, 1.2)	age, race, clinical site
						Baseline CD4 category (<200, 200-350, 350+) (blood test)	Started alcohol use trajectory among CD4 >350 vs. <200 at baseline	adjusted multinomial OR = 0.7 (0.5, 0.9)	
3	Du Bois et al. (2012)	Chicago, United States	HIV+ MSM in HIV care (n=945)	Clinic-based	Alcohol abuse (self- report; CAGE score)	HIV care adherence, past 12 months (self- report: no missed appointments)	HIV care adherence by alcohol use CAGE score	$\beta$ =.03, p-value = 0.019	race, sexual orientation, age, time since diagnosis, income, education, employment, medication/appointment adherence, depression, drug use, HIV treatment intervention group
4	Inciardi et al. (2005)	Miami, United States	Female sex workers (n=407)	Respondent- driven sampling	Alcohol use, past month (self-report)	HIV status (blood test)	Alcohol use among HIV+ vs. HIV- pre/post HIV testing	prevalence = 82.0% vs. 77.4%; p-value = NS	unadjusted
5	Jacob et al. (2013)	United States	HIV+ and matched HIV- veterans (n=7,422)	Clinic-based	Alcohol use level	HIV+ status known	Change in alcohol use pre/post known HIV+ status	% decreased = 46.7%, % increased = 18.6%, % no change = 22.8%, % started = 2.6%	unadjusted
					Alcohol use trajectories (self- report: AUDIT-C - severe chronic, severe nonchronic, late onset, young adult)	HIV status (blood test)	Alcohol use trajectory among HIV+ vs. HIV-	prevalence severe chronic = 47.8% vs. 52.2%; prevalence severe nonchronic = 43.5% vs. 56.5% (p- value = .083)	race, marital status, smoking, education, income
6	Kelso- Chichetto et al. (2018)	United States	HIV+ women (n=1123) and men (597)	Clinic-based (Women's Interagency HIV Study)	Moderate vs. low/no alcohol use, 10 years (self-report: group-based)	Unsuppressed VL (blood test: $\geq$ 200 copies/ml)	Moderate alcohol use trajectory among suppressed vs. unsuppressed VL <sup>†</sup>	adjusted OR = 0.55 (0.47, 0.64)	race, income, age, probable depression, drug use, BMI, diabetes, Framingham

No.	Author(s) (year)	Location	Population (n)	Sampling	Alcohol measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
				and Multicenter AIDS Cohort Study)	trajectory model)	Cumulative ART exposure, years (self- report)	Moderate alcohol use trajectory by cumulative ART exposure	adjusted OR = 1.02 (1.00, 1.05)	risk score
						Low CD4 <300 vs. ≥500 (blood test)	Moderate alcohol use trajectory among low vs. high CD4 count	adjusted OR women = 0.57 (0.45, 0.72); adjusted OR men = 0.46 (0.38, 0.55)	
7	Marshall et al. (2017)	United States	HIV+ veterans in care (n=3539)	Hospital- based (Veterans Aging Cohort Study)	Alcohol use trajectory (biomarker: PEth measures used to classify high vs. moderate risk)	HIV disease severity (VACS index: high or extreme vs. moderate)	HIV disease severity (high or extreme vs. moderate severity) among high (vs. moderate) alcohol use trajectories	adjusted OR (high disease severity) = 1.21 (0.89, 1.63); adjusted OR (extreme) = 1.83 (1.21, 2.78)	demographics, HAART at baseline, CD4, VL, HCV, smoking, IDU, depressive symptoms, homelessness
8	Monroe et al. (2016)	United States	HIV+ patients in care at CNICS clinics (n=9694)	Clinic-based	Heavy alcohol use, past 12 months (self-report: AUDIT-C >4 [men] or >3 [women] out of 12)	HIV care retention, past 12 months (medical records: IOM definition & visit adherence proportion)	HIV care retention among heavy vs. no drinking trajectories  Visit adherence among heavy vs. no drinking trajectories	adjusted OR = 0.78 (0.69, 0.88)  adjusted OR = 0.97 (0.91, 1.04)	drug use, panic symptoms, depression screen, sexual risk, age, race, IDU, CD4, VL, enrollment date, clinical site, panic symptoms and depression
9	Wang et al. (2018)	Guangxi, China	HIV+ persons (n=2964)	Population- based	Change in alcohol use after HIV diagnosis (self- report: increased vs. reduced vs. quit)	HIV diagnosis (self- report)  ART use (self-report)	Change in alcohol use pre/post HIV diagnosis  Reduction in alcohol use reduction among ART users vs. non-users	prevalence = 45.4% reduced, 19.5% quit, 2.5% increased  adjusted OR = 1.69 (1.30, 2.18)	age, sex, ethnicity, education, household income, employed

† denotes relationships that were transformed from the original publication to facilitate comparison across studies.

**Table 2.3 Longitudinal analyses of dietary behavior change by HIV continuum stage**

No.	Author(s) (year)	Location	Population (n)	Sampling	Dietary behavior measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
1	Collins et al. (2001)	United States	HIV+ persons in care (n=2,864)	Clinic-based, probability sample	Subjectively-rated healthy diet (self-report)	HIV diagnosis (self-report)	Change in healthy diet pre/post HIV diagnosis	sampling-weighted prevalence positive change in healthy diet = 60.4%	age, gender, ethnicity, marital status, education, drug use, CD4, symptom, self-rated health, physical functioning, stress and coping
2	Hendricks et al. (2008)	United States	HIV+ men (n=348)	Community-based	Dietary intake pattern, past 3 days (cluster analysis of self-reported food records: juice/soda vs. fast food vs. fruit/veg)	log(VL) (blood test)	log(VL) by dietary intake pattern	juice/soda vs. fast food dietary pattern: mean: mean log(VL) = 3.0 vs. 3.4; pairwise t-test p=0.008	age, race, energy intake per kilogram
						CD4 count (blood test)	CD4 count by dietary intake pattern	ANOVA p-value = NS	

45

**Table 2.4 Longitudinal analyses of sedentary behavior change by HIV continuum stage**

No.	Author(s) (year)	Location	Population (n)	Sampling	Sedentary behavior measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
1	Collins et al. (2001)	United States	HIV+ persons in care (n=2,864)	Clinic-based, probability sample	Regular exercise (self-report)	HIV diagnosis (self-report)	Change in regular exercise pre/post HIV diagnosis	sampling-weighted prevalence positive change in regular exercise = 43.6%	age, gender, ethnicity, marital status, education, drug use, CD4, symptom, self-rated health, physical functioning, stress and coping

**Table 2.5 Summary of study characteristics for all CVD risk behaviors**

	CVD risk behavior			
	Smoking	Alcohol use	Poor diet	Sedentary
<b>No. studies</b>	30 (100%)	54 (100%)	2 (100%)	6 (100%)
<b>Design</b>				
Longitudinal	7 (23%)	8 (15%)	2 (100%)	1 (17%)
Cross-sectional	23 (77%)	46 (85%)	0 (0%)	5 (83%)
<b>Sampling</b>				
Population-based	4 (13%)	5 (9%)	0 (0%)	1 (17%)
Hospital-/clinic-based	24 (80%)	35 (65%)	2 (100%)	4 (67%)
Community-based	1 (3%)	6 (11%)	0 (0%)	0 (0%)
Respondent-driven	1 (3%)	6 (11%)	0 (0%)	0 (0%)
Convenience	0 (0%)	2 (4%)	0 (0%)	1 (17%)
<b>Region</b>				
North America, Europe, Australia	22 (73%)	22 (41%)	2 (100%)	3 (50%)
Sub-Saharan Africa	3 (10%)	21 (39%)	0 (0%)	1 (17%)
South/Central America	0 (0%)	5 (9%)	0 (0%)	2 (33%)
Asia	4 (13%)	6 (11%)	0 (0%)	0 (0%)
Multiple	1 (3%)	0 (0%)	0 (0%)	0 (0%)
<b>CVD risk behavior measures</b>				
Biomarker	3 (10%)	1 (2%)	0 (0%)	0 (0%)
Self-report	27 (90%)	52 (96%)	2 (100%)	6 (100%)
Medical records	0 (0%)	1 (2%)	0 (0%)	0 (0%)

**Table 2.6 Summary of findings of longitudinal studies for all CVD risk behaviors**

	CVD risk behavior			
	Smoking	Alcohol use	Poor diet	Sedentary
<b>HIV continuum stage</b>				
HIV infection	+ (n=3)	+ (n=2)	No studies	No studies
HIV awareness	<b>M</b> (n=2)	- (n=1)	No studies	No studies
HIV treatment	- (n=2)	<b>M</b> (n=4)	- (n=1)	- (n=1)
HIV immune/viral recovery	No studies	- (n=1)	<b>0</b> (n=1)	No studies

Note: This table summarizes the findings of the systematic review for each CVD risk behavior by HIV continuum stage comparison. Effect estimates were harmonized across studies to enable comparisons (i.e., associations were reversed if variables were reverse-coded in a given study). Symbols indicate the predominant direction of association observed for all studies of that relationship: + = predominantly positive (causal); - = predominantly negative (protective); **0** = predominantly null; **M** = overall mixed findings.

## CHAPTER 3. PATTERNS OF CARDIOVASCULAR DISEASE RISK BEHAVIORS ACROSS THE HIV CONTINUUM: DATA FROM A POPULATION-BASED STUDY OF OLDER ADULTS IN RURAL SOUTH AFRICA

### 3.1. Abstract

**Background:** Mounting qualitative evidence suggests that people living with HIV (PLWH) adopt unhealthy cardiovascular disease (CVD) risk behaviors as a way to cope with the stress of living with HIV. However, few quantitative studies have been conducted to assess whether HIV causes adoption of CVD risk behaviors, let alone whether stress mediates this relationship. This study aimed to explore the patterns of three CVD risk behaviors, smoking, hazardous alcohol use and sedentary behavior across stages of the HIV continuum (HIV-negative, HIV-positive and unaware, HIV-positive aware and untreated, HIV-positive on treatment). In secondary analyses, we assessed whether various types of HIV-related physiological and psychological stress mediated the observed relationships.

**Methods:** Analyses were conducted using baseline data from a population-based cohort study of adults 40 years and older in rural Agincourt district in South Africa. HIV infection status was defined using dried blood spot HIV tests, and, among HIV-positive individuals, awareness and treatment status were defined using self-reported HIV status and detectable antiretroviral (ARV) drugs, respectively. CVD risk behaviors were defined using self-reported current smoking, hazardous alcohol use and sedentary behavior. Potential mediators of the relationship between HIV continuum stage and CVD risk behaviors included symptoms such as muscle weakness measured via grip strength test, and self-reported pain, physical dysfunction, cognitive impairments, and measures of psychological stress such as depressive symptoms and low subjective well-being. We estimated prevalence ratios (PR) and 95% confidence intervals (CI) for each CVD risk behavior across HIV continuum stage, in total and sex-stratified models. We

then tested whether there was evidence for mediation by also adjusting individually for each proposed mediator.

**Results:** A sample of n=4,061 participants were included in the study. The overall crude prevalence estimates of smoking, hazardous alcohol use and sedentary behaviors were 9%, 10%, and 30%, respectively. Compared to the HIV-negative group, the prevalence of smoking and hazardous alcohol use were both highest in the HIV-positive treated group: PR (95% CI) for smoking: 1.12 (0.66, 1.90); hazardous alcohol use: 1.10 (0.61, 1.96). The prevalence of sedentary behavior was highest in the HIV-positive unaware group: 1.10 (0.96, 1.28). None of these findings were statistically significant. We found no evidence of mediation, as none of the hypothesized mediators appreciably changed any effect estimates after controlling in adjusted models.

**Discussion:** The results of this study demonstrated that CVD risk behaviors were not significantly differently distributed across HIV continuum stage. Findings do not support the hypothesis that physiological and/or psychological stress mediates the relationship between HIV and CVD risk behaviors.

### **3.2. Introduction**

Since the introduction of antiretroviral therapy (ART), the survival of people living with HIV (PLWH) on treatment has approached that of the general population.<sup>1</sup> However, while total mortality has decreased, the proportion of deaths due to cardiovascular disease (CVD) has increased.<sup>2-5</sup> Numerous studies have shown that this is partly due to high prevalence of CVD risk behaviors among PLWH.<sup>6-15</sup> As a result, CVD prevention has become a health priority for HIV-positive populations, and treatment guidelines now recommend that clinicians routinely advise all HIV-positive persons to maintain a healthy lifestyle<sup>16</sup>, which consists of avoiding smoking and hazardous alcohol use, minimizing unhealthy diet and adopting more active lifestyles.<sup>17</sup>

CVD risk behaviors are of particular interest for older individuals living with HIV, since CVD is strongly associated with age.<sup>18</sup> Furthermore, older individuals comprise a fast-growing segment of the HIV-positive population, due to longer survival of PLWH on ART. As well, data demonstrate that such older populations remain at high risk of HIV acquisition due to failure of HIV prevention services to focus on this group and their having lower condom use and HIV testing rates as compared to younger people.<sup>19-22</sup> These trends are especially notable in the sub-Saharan African (SSA) region, which has the highest burden of HIV in the world and is undergoing drastic urbanization, associated with increases in sedentary behaviors and diets higher in processed foods.<sup>23, 24</sup> Currently, most HIV research and programs focus on adolescents and younger adults of reproductive age; thus further research on CVD risk behaviors among older PLWH in SSA is needed.

An important unresolved question is how HIV and CVD risk behaviors are related. CVD risk behaviors are frequently shown to be more prevalent among HIV-positive populations than the

general population.<sup>12, 25-29</sup> These differences often remain after controlling for known demographic and socioeconomic confounders, and have been replicated to varying degrees across populations. Yet, the underlying reasons have not been well-established. Unhealthy behaviors may operate as both antecedents and consequences of HIV, and much of the existing evidence is based on cross-sectional data, which cannot differentiate between the two pathways. Despite this, authors typically emphasize the role of CVD risk behaviors, particularly smoking and alcohol use, as antecedents of HIV. A growing body of qualitative evidence points, however, to the possibility that unhealthy behaviors can occur in response to HIV as a stress-coping mechanism, offering another plausible explanation. Put simply, PLWH often report feeling overwhelmed after receiving their HIV diagnosis<sup>30-33</sup> and adopting unhealthy behaviors as a form of relief or distraction from the stress of living with HIV.<sup>34-37</sup> In this context, HIV-related stress encompasses both the physiological symptoms of HIV, including pain<sup>38</sup>, weakness, physical dysfunction<sup>39-41</sup>, cognitive impairments<sup>42, 43</sup>, as well as its psychological symptoms, such as depressive symptoms<sup>44, 45</sup> and diminished subjective well-being.<sup>a</sup> While this is not an exhaustive list, it illustrates the profound physiological and psychological burdens that being HIV-positive can impose on an individual.<sup>46, 47</sup> Each of these is known to predict unhealthy behavior engagement in other disease contexts.<sup>48, 49</sup> Therefore, HIV-related stress, defined here as the physiological and psychological symptoms of HIV, may partly account for the elevated prevalence of CVD risk behaviors among PLWH and explain why they often persist despite intensive behavior modification efforts.<sup>9, 50-52</sup>

---

<sup>a</sup> The stress-coping theoretical framework is presented only briefly here but explicated in full detail in Chapter 1.

Under a stress-coping hypothesis, these physiological and psychological forms of stress would potentially act as mediators of a causal effect of HIV on CVD risk behaviors. Such mediation analyses may elucidate the underlying mechanisms and may also uncover clues regarding temporality. To illustrate, individuals may experience the physiological symptoms of HIV whether they are aware of their status or not; therefore, mediation pathways through physiological symptoms can plausibly operate among all HIV-infected individuals. In contrast, individuals can only experience psychological distress as a result of their infection after they know or suspect that they are HIV-positive; therefore, psychological stress-coping mechanisms can only operate among HIV-positive individuals who are aware of their status. Similarly, HIV-positive individuals who are on treatment, based on evidence of the salutary effects of ART on health and well-being of PLWH, would be expected to experience fewer physiological and psychological symptoms than those who are off treatment; therefore, both physiological and psychological stress-coping pathways would be attenuated among treated versus untreated individuals.

Assuming a mediation hypothesis is true, this suggests that physiological and psychological stress-coping pathways would operate differently at different stages of an HIV continuum that characterizes HIV infection, awareness and treatment status. Importantly, heterogeneity in outcomes would be obscured when using dichotomous measures, as has often been used in prior research (see Figure 3.1). Under the strong assumption that baseline CVD risk behaviors are similar across stages, observed differences in behavior prevalence by HIV continuum stage may be at least partly attributable to the consequences of HIV infection, awareness of infection and being on treatment, whereas lack of differences by stage would suggest against a mediation hypothesis. Thus, the HIV continuum approach may help disentangle mediation vs. confounding

pathways. Accordingly, we hypothesize that CVD risk behaviors would be least prevalent among HIV-negative individuals and most prevalent among HIV-positive individuals who are aware of their status but not on treatment.

To address these knowledge gaps, we explored the relationships between HIV continuum stage and three CVD risk behaviors among a population-based cohort of adults aged 40 years and over in rural Agincourt district in South Africa. As a secondary objective, we examined the potential mediating role of several measures of physiological and psychological stress in this relationship.

### **3.3. Methods**

#### **3.3.1. *Data source***

This study used baseline data from the Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa (HAALSI) study. The HAALSI study was designed to explore the individual, economic and contextual determinants of aging-related health conditions and overall well-being of older adults in a high HIV prevalence area. Recruitment was nested within the Agincourt Health and Demographic Surveillance System, from which a population-representative, sex-stratified random sample of 6,281 adults aged 40 years and over was drawn. One-fifth of sampled individuals were unable to or refused to participate in the study, yielding a total of n=5,059 participants who enrolled in the baseline cohort. This sample constituted approximately 20% of all eligible adults residing in Agincourt district at the time of recruitment.<sup>53</sup>

A survey questionnaire and physical examination were conducted and dried blood spot (DBS) samples were obtained from participants. Survey instruments were translated from English to the

local Shangaan language and back-translated to verify accuracy. Trained fieldworkers collected survey data using an interviewer-administered computer-assisted personal interview system on electronic tablets. Data were collected between November 2014 and November 2015 and have been made publicly available on the Harvard Dataverse website.<sup>54</sup> HAALSI was conducted by an interdisciplinary team of investigators at the Harvard School of Public Health and University of Witwatersrand in South Africa and ethical approvals were provided by each institution's IRB and the Mpumalanga Provincial Research and Ethics Committee. Eligibility for this analysis was restricted to individuals who consented to DBS testing and had complete data on all analytic variables described below (Figure 3.2).

### **3.3.2. Measures**

The main exposure was defined in two ways. Firstly, we created a dichotomous measure of HIV status (HIV-positive vs. HIV-negative) using results from DBS HIV testing. Secondly, we created a categorical HIV continuum stage variable (HIV-, HIV-positive but unaware, HIV-positive aware and untreated, and HIV-positive on treatment) using a combination of DBS HIV test results, detectable antiretroviral (ARV) drug levels (DBS samples were tested for FTC or 3TC as these two ARVs were used in all first and second-line ART regimens in South Africa at the time of the study), and self-reported lifetime diagnosis of HIV. HIV viral load results (dichotomized as  $>100$  vs.  $\leq 100$   $\log_{10}$  copies/ml) were used for sensitivity analyses by virologic suppression status among the HIV-positive on treatment group (see below).

Outcomes included three self-reported CVD risk behaviors, smoking, hazardous alcohol use and sedentary behavior. Smoking was defined using the question "*Do you currently smoke any tobacco products, such as cigarettes, cigars or pipes?*" Hazardous alcohol use was defined using

the Alcohol Use Disorders Identification Test (AUDIT-C), a screening tool that distinguishes hazardous from non-hazardous alcohol use based on self-reported alcohol use frequency, severity and binge drinking and has been validated in low-income settings.<sup>55, 56</sup> Hazardous alcohol use was classified using scores of >4 or >3 out of 12 total points for men and women, respectively, as per established guidelines.<sup>55, 56</sup> Sedentary behavior was defined using the International Physical Activity Questionnaire (IPAQ) score, a screening tool that classifies an individual's weekly physical activity level based on self-reported time spent doing vigorous or moderate physical activity or walking.<sup>57, 58</sup> Participants were classified as sedentary if they failed to meet any of the following criteria: 3+ days of vigorous activity at least 20 minutes per day, 5+ days of moderate activity or walking at least 30 minutes per day, or 5+ days of any combination of vigorous or moderate activity or walking achieving 600+ MET-minutes per week. IPAQ has been validated in low-income settings.<sup>58</sup> See Appendix Tables 5.7 and 5.8 for full details of AUDIT-C and IPAQ survey questions and scoring algorithms.

Potential mediators included four measures of physiological stress and two measures of psychological stress. Muscle strength was measured via grip strength tests performed in each hand. Scores were averaged across hands and used to classify muscle weakness using validated clinical thresholds for men and women (<37 kg and <23 kg, respectively).<sup>59</sup> Pain was assessed using the Brief Pain Inventory (BPI), a validated 11-item screening tool based on four questions regarding severity of pain in the past 24 hours and seven questions regarding the degree to which pain interferes with daily activities, each on a scale of 0-10.<sup>60, 61</sup> Mean scores were calculated separately for the severity and interference sub-scales and participants. Individuals with mean scores of 4 or greater on either sub-scale were classified as experiencing difficulties with pain. Physical dysfunction was defined as having difficulties performing activities of daily living

(ADLs) using the Katz Index of Independence in ADLs. Participants reported whether they could perform each of six ADLs (walking, sleeping, eating, bathing, getting in and out of bed, and using the toilet) without difficulties or assistance. Those who reported having difficulties or required assistance with at least one ADL were classified as experiencing physical dysfunction. Cognitive impairment was defined as having self-reported difficulties with memory, concentration, or learning new tasks. Each item was assessed using 5-point Likert scales, and individuals who reported having either fair/poor memory or moderate/severe/extreme difficulties with concentration or learning new tasks were classified as having cognitive impairments.

Two measures of psychological stress were defined as follows. We assessed depressive symptoms using the 8-item Center for Epidemiological Studies Depression scale (CESD-8), which is a widely used screening tool that has been validated in sub-Saharan African settings.<sup>62-</sup><sup>65</sup> Scores of >4 out of 8 total points were classified as elevated depressive symptoms. Lastly, low subjective well-being was assessed using two questions on life satisfaction “...*how satisfied are you with your life as a whole these days?*” and self-evaluated quality of life “*Please imagine a ladder... Suppose we say that the top of the ladder represents the best possible life for you and the bottom represents the worst possible life for you. On which step of the ladder would you say you personally feel you stand at this time?*” Both items were rated on 0-10 scales, the average of which was used as the subjective well-being score. Scores of  $\leq 5$  were classified as low subjective well-being. See Appendix Table 5.9 for detailed information on each survey question.

Potential confounders included demographic characteristics such as sex, age (continuous), education (completed primary education vs. lower educational attainment) and wealth (poorest 40% vs. other, using a household-based wealth index). In addition, variables on CVD history

were considered, including self-reported lifetime diagnosis or treatment for hypertension, dyslipidemia, diabetes, and self-reported lifetime occurrence of any of four cardiovascular events: myocardial infarction, stroke, angina or heart failure.

### **3.3.3. Analysis**

We described sample characteristics for all analytic variables. We then assessed the relationships between HIV status and each CVD risk behavior by fitting log-Poisson regression models to estimate prevalence ratios (PR) and 95% confidence intervals (CI) (generalized linear model with log link, Poisson distribution and robust standard errors).<sup>66, 67</sup> We further compared CVD risk behavior patterns by HIV continuum stage to assess if additional information was gained by stratifying by awareness and treatment status. We found that self-reported smoking and alcohol use was very low among females and thus also ran models stratified by sex.

In order to identify potential confounders, we constructed directed acyclic graphs (DAGs) for each of the hypothesized causal relationships to determine the minimal set of potential confounders sufficient for adjustment. Potential confounders were verified analytically using a  $p < 0.10$  threshold for significance and then included in models to estimate adjusted PRs (see Appendix Table 5.10 for bivariate analyses between each potential confounder and each exposure category and outcome). Unadjusted and adjusted analyses were compared to assess the degree of bias due to confounding.

We then examined whether there was evidence for mediation via each hypothesized mediator. Using standard mediation analysis methods, we first tested the significance of each of the exposure-mediator and mediator-outcome relationships (i.e., the indirect pathways).<sup>68</sup> We then

estimated direct effects by comparing point estimates from the adjusted models above (total effects) with models additionally adjusting for each proposed mediator (direct effects). Point estimates that moved towards the null were considered consistent with a mediation hypothesis. All analyses were performed using Stata version 15.1 (Stata Corp, College Station, TX, USA).

#### **3.3.4. Sensitivity analyses**

**Missing data.** We were unable to determine HIV continuum stage among 9% of participants, primarily due to refusal to provide DBS specimen (n=352, 7%). Missing data on survey variables was minimal, since surveys were administered using electronic tablets which forced responses. Nonetheless, missing data were observed among 2-3% of participants on variables related to subjective well-being, pain and cognitive impairment variables, as a result of “don’t know” or “refused” responses. Data on muscle weakness were also missing for 7% of participants who did not complete the physical exam. We explored the impact of missing data by conducting sensitivity analyses using multiple imputation (MI) via chained equations to impute missing values. We elected not to impute missing HIV status since it is well-documented that individuals who know they are HIV-positive have been noted to be more likely to refuse testing, thus missing data were unlikely to meet the requisite missing at random assumption.<sup>69</sup> Sample characteristics were compared between the “complete case sample” used in main analyses (n=4,061) and those missing data only on HIV continuum stage, referred to hereafter as the “MI sample” (n=4,610). We then examined whether the results from complete case and MI analyses substantially differed.

**Exposure operationalization.** We also explored whether results were sensitive to how HIV continuum stage was operationalized. Results of the main analysis were compared to those from

three scenarios using alternative exposure definitions. In scenario 1, we aimed to address the potential for known HIV-positive individuals to falsely report being HIV-negative. Individuals who were initially classified as HIV-positive and unaware but who had reported having their last HIV test six or more months previously and had a detectable HIV viral load test ( $>2 \log_{10}$  copies/mL) were assumed to in fact know their status. We re-classified these individuals from HIV-positive unaware to HIV-positive aware untreated and compared results. In scenario 2, we used self-reported ART use as well as detectable ARVs to classify individuals as HIV-positive on treatment. Compared to detectable ARVs alone, this more inclusive measure of treatment status aimed to account for possible momentary ART non-adherence at the time of the test. In scenario 3, we explored whether failure to achieve viral suppression among those with detectable ARVs was associated with unhealthy behaviors, since those experiencing treatment failure may feel sicker than those whose virus is suppressed. We examined whether outcomes among the HIV+ on treatment group varied by viral suppression ( $<2 \log_{10}$  copies/ml), which was achieved by 72% of those with detectable ARVs.

### **3.4. Results**

#### ***3.4.1. Participant characteristics***

Of the  $n=4,061$  participants in this study, 46% were male, 52% were over age 60, and less than one-fifth completed primary education or were employed (Table 3.1). HIV prevalence was 25%, though only 17% self-reported being HIV+. Among those who tested HIV-positive, 64% had detectable ARVs. These data showed that 3,038 (75%) were in the HIV-negative group, 275 (7%) were in the HIV-positive unaware group, 93 (2%) were in the HIV-positive aware untreated group, and 655 (16%) were in the HIV-positive on treatment group. The overall

prevalence estimates of smoking, hazardous alcohol use and sedentary behavior were 9%, 10%, and 44%, respectively. Over one-third of participants self-reported awareness of hypertension diagnosis, 13% dyslipidemia diagnosis and 7% diabetes diagnosis. The most prevalent symptoms reported were muscle weakness (66%), cognitive impairments (42%) and low subjective well-being (29%). Differences by sex were notable for smoking and hazardous alcohol use, which were reported by very few women. Some covariates such as being married and experiencing muscle weakness were also more common among men.

### ***3.4.2. CVD risk behavior patterns***

**Overall sample.** Table 3.2 shows PRs and 95% CIs for each CVD risk behavior by HIV status. In unadjusted analyses, HIV-positive versus HIV-negative status was associated with higher prevalence of smoking: PR (95% CI) = 1.23 (1.03, 1.46); no difference in hazardous alcohol use: 1.00 (0.83, 1.21); and lower prevalence of sedentary behavior: 0.85 (0.78, 0.93). Bivariate analyses showed that sex, age, education, employment, marital status, wealth, hypertension, dyslipidemia and diabetes all met criteria for confounding and were thus included as confounders in all analyses (Appendix Table 5.10). After adjusting for confounders, the association between HIV+ status and smoking was attenuated and no longer statistically significant: PR (95% CI) = 1.10 (0.90, 1.34), and the associations between HIV+ status and hazardous alcohol use and sedentary behaviors did not change: 0.95 (0.78, 1.15) and 0.89 (0.81, 0.97), respectively. Table 3.2 also shows PRs and 95% CIs for each CVD risk behavior by HIV continuum stage, using the HIV-negative group as the reference category. We found that the HIV-positive aware untreated group had the highest prevalence of smoking and hazardous alcohol use, though none of the associations reached statistical significance in unadjusted or adjusted models. The HIV-positive on treatment group had the lowest prevalence of sedentary behaviors in unadjusted analyses: PR

(95% CI) = 0.79 (0.70, 0.88), but this association did not remain significant in the adjusted model. Predicted prevalence estimates are calculated from the regression model after adjustment for confounders and displayed in Figure 3.3.

**Sex-stratified models.** Results from sex-stratified models showed that effect estimates among males were generally similar to those among all participants. Compared to the HIV-negative reference group, the prevalence of smoking was significantly higher in the HIV-positive aware untreated group: PR (95% CI) = 1.64 (1.01, 2.67), and the prevalence of hazardous alcohol use was higher in the HIV-positive unaware group: 1.45 (1.00, 2.09), but these associations did not remain significant in adjusted analyses. Among females, there were almost no self-reported smokers in the HIV-positive unaware and HIV-positive aware untreated groups thus PRs for smoking were both 0.0. In adjusted analyses, the HIV-positive aware untreated group had the highest prevalence of hazardous alcohol use: PR (95% CI) = 2.72 (1.04, 7.09). Predicted prevalence estimates are displayed graphically in Figure 3.4 by males and females (numerical results are reported in Appendix Table 5.11).

### **3.4.3. Mediation analyses**

The unadjusted prevalence of each hypothesized mediator is reported in Table 3.3 by HIV continuum stage and outcome status. Contrary to our hypothesis, none of the proposed mediators were more common among HIV-positive versus HIV-negative groups. Furthermore, the prevalence of each proposed mediator was generally similar among HIV-positive groups, irrespective of awareness or treatment status. However, these patterns reversed after controlling for age (data not shown). Muscle weakness was associated with higher prevalence of smoking and hazardous alcohol use, but the other proposed mediators were either inversely associated or

not associated with smoking. All proposed mediators were positively associated with sedentary behavior.

Results from mediation analysis models are reported in Table 3.4 and displayed graphically in Figure 3.5. Total effects (using adjusted models above) were not statistically significant prior to testing for mediation, and point estimates did not change appreciably after controlling for any physiological or psychological symptom.

#### **3.4.4. Sensitivity analyses**

Sensitivity analyses using MI demonstrated no significant changes in point estimates or CIs as compared to the main analysis among complete cases only (Table 3.5). Results from the three alternative exposure definitions scenarios are shown in Table 3.6. The main analysis represents the adjusted model above. In scenario 1, we re-classified 21 individuals from being HIV-positive unaware to HIV-positive aware untreated based on having received HIV testing at least 6 months prior to the study and a detectable viral load; results were not appreciably different from the base case model. In scenario 2, we re-classified 45 individuals from being HIV-positive aware untreated to HIV-positive on treatment based on self-reported ART use. Smoking and hazardous alcohol use were no longer highest in the HIV+ aware untreated group, though the revised estimates remained non-significant. Finally, in scenario 3 we generated a new category for virally suppressed, which included 484 individuals. Results differed slightly between the HIV-positive on treatment and HIV-positive virally suppressed groups; notably, the HIV-positive on treatment (non-suppressed) group was associated with higher smoking and HIV-positive virally

suppressed group was associated with lower smoking. However, none of the observed differences were statistically significant before or after stratifying by viral suppression.

### **3.5. Discussion**

In this study, we examined the relationships between HIV and three CVD risk behaviors among a rural sample of older adults in South Africa. We found that HIV continuum stage was not significantly associated with smoking, hazardous alcohol use or sedentary behaviors. However, point estimates of the prevalence of smoking and hazardous alcohol use were highest among individuals in the HIV-positive aware untreated group, which is consistent with our *a priori* hypothesis that this group would be most likely to engage in unhealthy behaviors. Comparing HIV-positive versus HIV-negative individuals, i.e., ignoring awareness and treatment status as is often done in other studies, we observed that HIV infection status was not significantly associated with smoking and hazardous alcohol use and associated with lower prevalence of sedentary behaviors. These findings are not consistent with prior studies, which have generally observed drastically elevated CVD risk behaviors among HIV-positive versus HIV-negative individuals.<sup>6-15, 25-29</sup> However, while our results did not achieve statistical significance, point estimates suggest 10% increased prevalence of smoking among HIV-positive versus HIV-negative individuals.

Some findings varied by sex of the participants. However, differences by sex were largely driven by extremely low overall prevalence of smoking and hazardous alcohol use among women. In our sample, 20% of men and <1% of women self-reported smoking; thus the model for smoking among women was largely uninformative. Likewise, hazardous alcohol use was reported by 16% of men and only 4% of women. Patterns of hazardous alcohol use across HIV continuum stage

differed by sex, with highest prevalence being observed in the HIV-positive aware untreated group among women, and in the HIV-positive unaware group among men. It remains unclear why alcohol use patterns differed between men and women, though it is possible that men's and women's behavioral responses to HIV differ in this setting. However, since baseline prevalence was higher among men, larger relative differences in outcome prevalence by HIV continuum stage would have been necessary for significant findings to emerge among men than women.

The overall and sex-stratified CVD risk behavior prevalences observed in our study are similar to other population-based studies conducted in this setting. The first South Africa National Health and Nutrition Examination Survey (SA NHANES) estimated an overall smoking prevalence of 15.3% (95% CI: 12.0%, 19.4%) in Mpumalanga Province, with 28.7% (22.9%, 35.3%) among males and 3.6% (2.2%, 5.8%) among females.<sup>70</sup> Similarly, the South African National HIV, Incidence, Behaviour and Communication (SABSSM) 2008 survey. estimated the prevalence of hazardous alcohol use to be 9% (Males: 17%; Females: 2.9%).<sup>71</sup> Nationally-representative data from the Global Ageing and Adult Health (SAGE) survey in South Africa found that 42% of adults 18 years or older were sedentary (defined as physically inactive using the Global Physical Activity Questionnaire)<sup>72</sup>, similar to 47% overall prevalence of sedentary behavior in this study. However, unlike in the current study, significant differences were found by HIV status. One study conducted among chronic care patients in North West Province, South Africa estimated the prevalence of hazardous alcohol use to be 12.9% vs. 6.0% among HIV-positive vs. HIV-negative individuals.<sup>73</sup> One explanation is that previous studies may have been biased by restricting participation to clinic-based samples. In addition, these studies were not restricted to older adults; thus, our null findings may simply reflect unique characteristics of the aging population in this setting.

In mediation analyses, the patterns of proposed mediators across HIV continuum stages were not consistent with what we hypothesized *a priori*. We expected to see greater physiological symptoms between HIV-positive vs. HIV-negative individuals, and greater psychological symptoms between HIV-positive aware vs. unaware individuals. In fact, all proposed mediators (i.e., muscle weakness, pain, physical dysfunction, cognitive impairment, depressive symptoms and low subjective well-being) were either less prevalent or no different between HIV-positive vs. HIV-negative groups, irrespective of awareness and treatment status. Since it is unlikely that HIV acquisition or diagnosis alleviates these symptoms, this suggests that they were likely to be antecedents, rather than consequences, of HIV acquisition. For example, those experiencing pain and weakness may have been less sexually active and thus had lower risk of acquiring HIV. This hypothesis is further supported by the fact that most symptoms as measured in this study were associated with age – symptomatic individuals were more likely to be both older and HIV-uninfected.

The estimated prevalence ratios did not change appreciably after adjusting for any of the proposed mediators, failing to provide support for our mediation hypothesis. It is possible that residual biases may explain null findings if, for example, individuals with better self-care behaviors are more likely to seek HIV testing (confounding) or agree to participate in the study (selection). Critically, however, since the mediation pathways were expected to vary across HIV continuum stages, these biases would have also had to operate differentially by stage in the opposite direction in order to produce the null findings we observed. It is therefore unlikely that we would have observed these null findings if the mediation pathways did in fact exist via the proposed stress measures in this study. However, we remain unable to rule out other alternative explanations.

First, the aforementioned temporality concerns regarding the exposure-outcome relationship equally apply to the mediator-exposure and mediator-outcome relationships. In addition, we cannot assume monotonic effects, i.e., HIV-related symptoms may encourage some individuals to adopt healthier behaviors rather than risk behaviors for CVD. If symptoms are causal in some individuals and protective in others, we would only observe net effects averaged across individuals, obscuring mediation effects. It is worth noting that several prior studies have tested the relationship between HIV and CVD risk behaviors and found that symptoms, such as depression, met statistical criteria for confounding.<sup>74-76</sup> In these studies, the authors rarely described, let alone tested, these symptoms as potential mediators; however, to the extent that temporality could not be established, these findings could be consistent with confounding or mediation mechanisms.

### ***3.5.1. Limitations***

This study has several key limitations. First and foremost, the cross-sectional nature of the data hindered our ability to establish temporality of the relationships between exposures, mediators and outcomes. We addressed this limitation by hypothesizing specific mediation pathways that would operate differently for physiological and psychological symptoms across HIV continuum stages, and leveraging the inherent sequential ordering of the HIV continuum to help distinguish between mediation vs. confounding effects. Observed symptom patterns across stage were not consistent with our mediation hypothesis, but CVD risk behavior patterns suggested that accounting for awareness and treatment status yielded additional information. For example, compared to the HIV-negative group, smoking prevalence was estimated to be 40% higher in the HIV-positive aware untreated group but only 7% and 15% higher in the HIV-positive unaware and HIV-positive on treatment groups, respectively, findings that would have been missed if

comparing by HIV infection status alone. However, the sample sizes in this study were too small to detect even modest effect sizes across HIV continuum stage, especially since the prevalence of untreated infection is low among those who were aware of their HIV status.

Second, the use of self-reported measures raises potential concerns with measurement error. We had no information on adherence or length of time since treatment initiation; thus, our definition of being on treatment assumes everyone on treatment was adherent and would have had detectable ARVs as per DBS testing. Additionally, HIV status may be underreported due to its sensitive nature and fear of stigma and discrimination. Sensitivity analyses found that few participants would have been re-classified based on several likely misclassification scenarios, and findings were not sensitive to such changes.

Third, while the proposed mediators are known to be associated with HIV, at best they are proxies of HIV-related stress. Specifically, these variables represent various manifestations of HIV in the forms of physiological discomforts or disabilities, or negative cognitive or emotional states that are indicative of feeling stressed. However, the available measures were not HIV-specific; thus, we could not determine whether individuals feeling depressed, for example, were depressed due to being HIV-positive or some other cause. We also lacked other likely stress-coping pathways, notably via symptoms of anxiety or experiences or feelings of stigma. Ideal measures of stress could include salivary or hair cortisol levels, which quantify cumulative exposures to chronic stress.<sup>77</sup> However, it would still be fundamentally difficult to determine whether the stress experienced by an individual actually prompted them to engage in unhealthy behaviors or stymied their efforts to avoid them, i.e., whether the behavior was a coping behavior or not.

Fourth, about 20% of the overall cohort was not included in this study due to missing data, most notably the 7% who refused consent to participate in DBS testing. Fortunately, most other missing data were minimal, and while the distributions of most variables were significantly different between complete case vs. MI samples (the complete case sample was slightly younger and less symptomatic), most differences were within 2% and therefore not likely to have affected our findings (Appendix Tables 5.12 and 5.13). Sensitivity analyses comparing complete case and MI analyses did not suggest that selection bias was present. Point estimates and CIs from MI analyses were not meaningfully different from those in complete case analyses; nonetheless, this assumption cannot be tested empirically using the observed data. Potential for selection bias was likely mitigated by the population-based sampling approach, which ensured representation of uninfected, undiagnosed and out-of-care populations, who are often omitted by design in clinic-based samples.

Finally, we cannot rule out residual confounding from other predictors of HIV acquisition, testing and treatment, including health-seeking tendencies that would influence unhealthy behavior engagement and access to care. As a result, individuals at different HIV continuum stages may differ on other common causes of HIV-related stress and CVD risk behaviors that were not captured in this study. Other unmeasured contextual factors, including social norms and health messaging unique to this population and setting may also limit generalizability to other populations.

### **3.6. Conclusion**

This study explored the relationships between HIV and CVD risk behaviors among a population-based sample of older adults living in a rural, high HIV prevalence area in South Africa. Our

findings provide evidence that CVD risk behaviors were not associated with HIV continuum stage among the older adult population, suggesting that behavioral modification interventions may be best targeted towards the general population. This study was also the first to our knowledge to conduct mediation analyses to test this stress-coping hypothesis among the older African population. Our findings do not provide supportive evidence for mediation; however, these analyses would need to be replicated in other populations and using longitudinal data.

### 3.7. References

1. Palella, F.J., Jr., K.M. Delaney, A.C. Moorman, et al., *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.* N Engl J Med, 1998. **338**(13): p. 853-60.
2. Sackoff, J.E., D.B. Hanna, M.R. Pfeiffer, et al., *Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City.* Ann Intern Med, 2006. **145**(6): p. 397-406.
3. Clark, S.J., F.X. Gomez-Olive, B. Houle, et al., *Cardiometabolic disease risk and HIV status in rural South Africa: establishing a baseline.* BMC Public Health., 2015. **15:135**.(doi): p. 10.1186/s12889-015-1467-1.
4. Wada, N., L.P. Jacobson, M. Cohen, et al., *Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome-negative individuals followed simultaneously in long-term cohort studies, 1984-2008.* Am J Epidemiol, 2013. **177**(2): p. 116-25.
5. Hanna, D.B., C. Ramaswamy, R.C. Kaplan, et al., *Trends in Cardiovascular Disease Mortality Among Persons With HIV in New York City, 2001-2012.* Clin Infect Dis, 2016. **63**(8): p. 1122-1129.
6. Glass, T.R., C. Ungsedhapand, M. Wolbers, et al., *Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study.* HIV Med, 2006. **7**(6): p. 404-10.
7. Lifson, A.R. and H.A. Lando, *Smoking and HIV: prevalence, health risks, and cessation strategies.* Curr HIV/AIDS Rep, 2012. **9**(3): p. 223-30.
8. Mdodo, R., E.L. Frazier, S.R. Dube, et al., *Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys.* Ann Intern Med, 2015. **162**(5): p. 335-44.
9. Kelso, N.E., D.S. Sheps, and R.L. Cook, *The association between alcohol use and cardiovascular disease among people living with HIV: a systematic review.* Am J Drug Alcohol Abuse, 2015. **41**(6): p. 479-88.
10. Weinberger, A.H., P.H. Smith, A.P. Funk, et al., *Sex Differences in Tobacco Use Among Persons Living With HIV/AIDS: A Systematic Review and Meta-Analysis.* J Acquir Immune Defic Syndr., 2017. **74**(4): p. 439-453. doi: 10.1097/QAI.0000000000001279.

11. Shiau, S., S.M. Arpadi, M.T. Yin, et al., *Patterns of drug use and HIV infection among adults in a nationally representative sample*. *Addict Behav.*, 2017. **68:39-44**.(doi): p. 10.1016/j.addbeh.2017.01.015. Epub 2017 Jan 7.
12. Fisher, J.C., H. Bang, and S.H. Kapiga, *The association between HIV infection and alcohol use: a systematic review and meta-analysis of African studies*. *Sex Transm Dis*, 2007. **34**(11): p. 856-63.
13. Galvan, F.H., E.G. Bing, J.A. Fleishman, et al., *The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study*. *J Stud Alcohol.*, 2002. **63**(2): p. 179-86.
14. Joy, T., H.M. Keogh, C. Hadigan, et al., *Dietary fat intake and relationship to serum lipid levels in HIV-infected patients with metabolic abnormalities in the HAART era*. *AIDS.*, 2007. **21**(12): p. 1591-600. doi: 10.1097/QAD.0b013e32823644ff.
15. Schafer, J., J. Young, A. Calmy, et al., *High prevalence of physical inactivity among patients from the Swiss HIV Cohort Study*. *AIDS Care.*, 2017. **29**(8): p. 1056-1061. doi: 10.1080/09540121.2016.1274016. Epub 2017 Jan 5.
16. European AIDS Clinical Society, *EACS guidelines for the treatment of adult HIV-positive persons*. 2017, EACS.
17. Aberg, J.A., *Cardiovascular complications in HIV management: past, present, and future*. *J Acquir Immune Defic Syndr*, 2009. **50**(1): p. 54-64.
18. Vollmer, S., K. Harttgen, T. Alfvén, et al., *The HIV Epidemic in Sub-Saharan Africa is Aging: Evidence from the Demographic and Health Surveys in Sub-Saharan Africa*. *AIDS Behav*, 2016.
19. Johnson, L.F., T.M. Rehle, S. Jooste, et al., *Rates of HIV testing and diagnosis in South Africa: successes and challenges*. *AIDS.*, 2015. **29**(11): p. 1401-9. doi: 10.1097/QAD.0000000000000721.
20. Negin, J., B. Nemser, R. Cumming, et al., *HIV attitudes, awareness and testing among older adults in Africa*. *AIDS Behav.*, 2012. **16**(1): p. 63-8. doi: 10.1007/s10461-011-9994-y.
21. Vollmer, S., T. Alfvén, J. Padayachy, et al., *HIV surveys in older adults: better data, better health*. *Lancet HIV.*, 2015. **2**(2): p. e40-1. doi: 10.1016/S2352-3018(15)00004-1. Epub 2015 Jan 29.

22. Rosenberg, M.S., F.X. Gomez-Olive, J.K. Rohr, et al., *Sexual Behaviors and HIV Status: A Population-Based Study Among Older Adults in Rural South Africa*. *J Acquir Immune Defic Syndr.*, 2017. **74**(1): p. e9-e17.
23. UNAIDS, *Global report: UNAIDS report on the global AIDS epidemic 2013*. 2013: Geneva, Switzerland.
24. Bain, L.E., A.P. Kum, N.C. Ekukwe, et al., *HIV, cardiovascular disease, and stroke in sub-Saharan Africa*. *Lancet HIV*, 2016. **3**(8): p. e341-2.
25. Tesoriero, J.M., S.M. Gieryic, A. Carrascal, et al., *Smoking among HIV positive New Yorkers: prevalence, frequency, and opportunities for cessation*. *AIDS Behav*, 2010. **14**(4): p. 824-35.
26. Crane, H.M., M.E. McCaul, G. Chander, et al., *Prevalence and Factors Associated with Hazardous Alcohol Use Among Persons Living with HIV Across the US in the Current Era of Antiretroviral Treatment*. *AIDS Behav*, 2017. **11**(10): p. 017-1740.
27. Ikeda, M.L., N.T. Barcellos, P.R. Alencastro, et al., *Alcohol Drinking Pattern: A Comparison between HIV-Infected Patients and Individuals from the General Population*. *PLoS One.*, 2016. **11**(6): p. e0158535. doi: 10.1371/journal.pone.0158535. eCollection 2016.
28. Schuelter-Trevisol, F., F.H. Wolff, P.R. Alencastro, et al., *Physical activity: do patients infected with HIV practice? How much? A systematic review*. *Curr HIV Res.*, 2012. **10**(6): p. 487-97.
29. Mdege, N.D., S. Shah, O.A. Ayo-Yusuf, et al., *Tobacco use among people living with HIV: analysis of data from Demographic and Health Surveys from 28 low-income and middle-income countries*. *Lancet Glob Health.*, 2017. **5**(6): p. e578-e592. doi: 10.1016/S2214-109X(17)30170-5.
30. Reynolds, N.R., *Cigarette smoking and HIV: more evidence for action*. *AIDS Educ Prev.*, 2009. **21**(3 Suppl): p. 106-21. doi: 10.1521/aeap.2009.21.3\_suppl.106.
31. Grover, K.W., A. Gonzalez, and M.J. Zvolensky, *HIV symptom distress and smoking outcome expectancies among HIV+ smokers: a pilot test*. *AIDS Patient Care STDS.*, 2013. **27**(1): p. 17-21. doi: 10.1089/apc.2012.0333.
32. Tsui, J.I., D.M. Cheng, S.M. Coleman, et al., *Pain and Risk Behaviors Among HIV-Infected Persons in St. Petersburg, Russia*. *AIDS Behav.*, 2017. **21**(6): p. 1775-1781. doi: 10.1007/s10461-016-1593-5.

33. Weinberger, A.H., E.K. Seng, J.W. Ditre, et al., *Perceived interrelations of pain and cigarette smoking in a sample of adult smokers living with HIV/AIDS*. *Nicotine Tob Res*, 2018. **31**(4830708).
34. Elliott, J.C., E. Aharonovich, A. O'Leary, et al., *Drinking motives among HIV primary care patients*. *AIDS Behav.*, 2014. **18**(7): p. 1315-23. doi: 10.1007/s10461-013-0644-4.
35. Akhtar-Khaleel, W.Z., R.L. Cook, S. Shoptaw, et al., *Trends and Predictors of Cigarette Smoking Among HIV Seropositive and Seronegative Men: The Multicenter Aids Cohort Study*. *AIDS Behav.*, 2016. **20**(3): p. 622-32. doi: 10.1007/s10461-015-1099-6.
36. Webb, M.S., P.A. Vanable, M.P. Carey, et al., *Cigarette smoking among HIV+ men and women: examining health, substance use, and psychosocial correlates across the smoking spectrum*. *J Behav Med.*, 2007. **30**(5): p. 371-83. Epub 2007 Jun 15.
37. Garey, L., J. Bakhshaie, C. Sharp, et al., *Anxiety, depression, and HIV symptoms among persons living with HIV/AIDS: the role of hazardous drinking*. *AIDS Care*, 2015. **27**(1): p. 80-5. doi: 10.1080/09540121.2014.956042. Epub 2014 Sep 16.
38. Ferrari, S., S. Vento, S. Monaco, et al., *Human immunodeficiency virus-associated peripheral neuropathies*. *Mayo Clin Proc.*, 2006. **81**(2): p. 213-9. doi: 10.4065/81.2.213.
39. Rosen, S., M. Ketlhapile, I. Sanne, et al., *Differences in normal activities, job performance and symptom prevalence between patients not yet on antiretroviral therapy and patients initiating therapy in South Africa*. *Aids*, 2008. **22 Suppl 1**: p. S131-9.
40. O'Brien, K.K., A.M. Bayoumi, C. Strike, et al., *Exploring disability from the perspective of adults living with HIV/AIDS: development of a conceptual framework*. *Health Qual Life Outcomes*, 2008. **6**: p. 76.
41. Schrack, J.A., L.P. Jacobson, K.N. Althoff, et al., *Effect of HIV-infection and cumulative viral load on age-related decline in grip strength*. *Aids*, 2016. **30**(17): p. 2645-2652.
42. Seider, T.R., X. Luo, A. Gongvatana, et al., *Verbal memory declines more rapidly with age in HIV infected versus uninfected adults*. *J Clin Exp Neuropsychol*, 2014. **36**(4): p. 356-67.
43. Harrison, J.D., J.A. Dochney, S. Blazekovic, et al., *The nature and consequences of cognitive deficits among tobacco smokers with HIV: a comparison to tobacco smokers without HIV*. *J Neurovirol.*, 2017. **23**(4): p. 550-557. doi: 10.1007/s13365-017-0526-z. Epub 2017 Apr 20.

44. Dube, B., T. Benton, D.G. Cruess, et al., *Neuropsychiatric manifestations of HIV infection and AIDS*. J Psychiatry Neurosci, 2005. **30**(4): p. 237-46.
45. Hinkin, C.H., S.A. Castellon, J.H. Atkinson, et al., *Neuropsychiatric aspects of HIV infection among older adults*. J Clin Epidemiol, 2001. **54 Suppl 1**: p. S44-52.
46. Reis, A.C., M.N. Guerra, and L.M. Lencastre, *Treatment adherence and subjective well-being in HIV/AIDS infection*. AIDS Care, 2013. **25**(12): p. 1604-11.
47. Greeff, M., L.R. Uys, D. Wantland, et al., *Perceived HIV stigma and life satisfaction among persons living with HIV infection in five African countries: a longitudinal study*. Int J Nurs Stud., 2010. **47**(4): p. 475-86. doi: 10.1016/j.ijnurstu.2009.09.008. Epub 2009 Oct 24.
48. Kelly, K.M., R. Bhattacharya, S. Dickinson, et al., *Health Behaviors Among Breast Cancer Patients and Survivors*. Cancer Nurs., 2015. **38**(3): p. E27-34. doi: 10.1097/NCC.0000000000000167.
49. Browning, K.K., M.E. Wewers, A.K. Ferketich, et al., *The Self-regulation Model of Illness applied to smoking behavior in lung cancer*. Cancer Nurs., 2009. **32**(4): p. E15-25. doi: 10.1097/NCC.0b013e3181a0238f.
50. Miguez-Burbano, M.J., J.E. Lewis, and R. Malow, *Alcohol and race/ethnicity elicit different changes in lipid profiles in HIV-infected individuals receiving highly active antiretroviral therapy*. J Assoc Nurses AIDS Care, 2009. **20**(3): p. 176-83.
51. Nicholas, P.K., J.G. Voss, I.B. Corless, et al., *Unhealthy behaviours for self-management of HIV-related peripheral neuropathy*. AIDS Care., 2007. **19**(10): p. 1266-73.
52. Pool, E.R., O. Dogar, R.P. Lindsay, et al., *Interventions for tobacco use cessation in people living with HIV and AIDS*. Cochrane Database Syst Rev., 2016(6): p. CD011120. doi: 10.1002/14651858.CD011120.pub2.
53. Kahn, K., M.A. Collinson, F.X. Gomez-Olive, et al., *Profile: Agincourt health and socio-demographic surveillance system*. Int J Epidemiol., 2012. **41**(4): p. 988-1001.
54. Harvard Center for Population and Development Studies, *HAALSI Baseline Survey*. 2016: Harvard Dataverse, V1.
55. Seth, P., M. Glenshaw, J.H. Sabatier, et al., *AUDIT, AUDIT-C, and AUDIT-3: drinking patterns and screening for harmful, hazardous and dependent drinking in Katutura, Namibia*. PLoS One, 2015. **10**(3): p. e0120850.

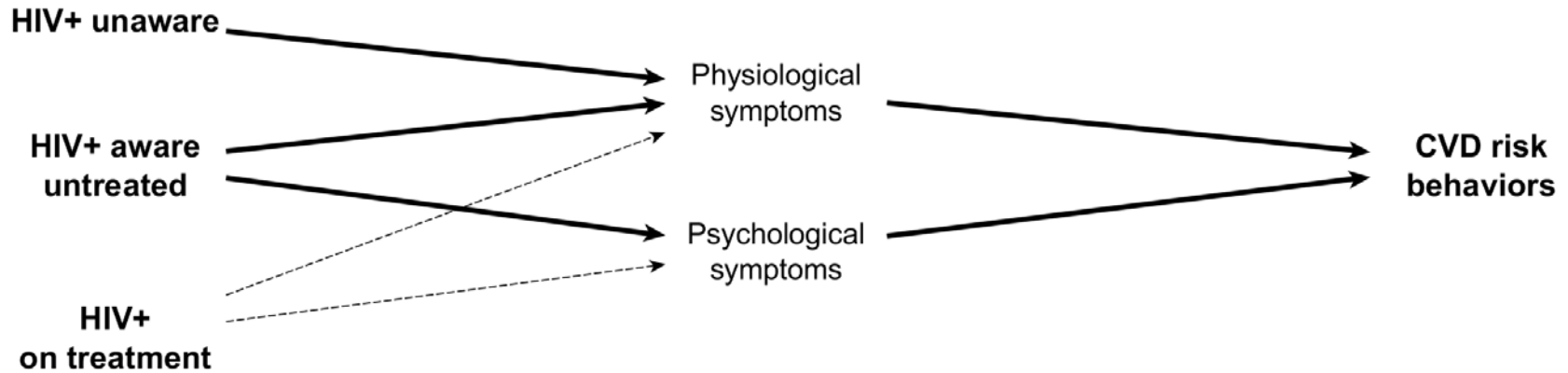
56. Bush, K., D.R. Kivlahan, M.B. McDonell, et al., *The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test.* Arch Intern Med., 1998. **158**(16): p. 1789-95.
57. Lee, P.H., D.J. Macfarlane, T.H. Lam, et al., *Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review.* Int J Behav Nutr Phys Act., 2011. **8:115**.(doi): p. 10.1186/1479-5868-8-115.
58. Oyeyemi, A.L., U.M. Bello, S.T. Philemon, et al., *Examining the reliability and validity of a modified version of the International Physical Activity Questionnaire, long form (IPAQ-LF) in Nigeria: a cross-sectional study.* BMJ Open., 2014. **4**(12): p. e005820. doi: 10.1136/bmjopen-2014-005820.
59. Sallinen, J., S. Stenholm, T. Rantanen, et al., *Hand-grip strength cut points to screen older persons at risk for mobility limitation.* J Am Geriatr Soc, 2010. **58**(9): p. 1721-6.
60. Furler, L., *[Validity and reliability of the pain questionnaire "Brief Pain Inventory". A literature research].* Pflege Z., 2013. **66**(9): p. 546-50.
61. Sharma, A., D.R. Hoover, Q. Shi, et al., *Frequent Occurrence of Pain and Prescription Opioid Use for Treatment of Pain Among Women with and at Risk for HIV Infection.* AIDS Behav, 2017. **19**(10): p. 017-1828.
62. Baron, E.C., T. Davies, and C. Lund, *Validation of the 10-item Centre for Epidemiological Studies Depression Scale (CES-D-10) in Zulu, Xhosa and Afrikaans populations in South Africa.* BMC Psychiatry., 2017. **17**(1): p. 6. doi: 10.1186/s12888-016-1178-x.
63. Chishinga, N., E. Kinyanda, H.A. Weiss, et al., *Validation of brief screening tools for depressive and alcohol use disorders among TB and HIV patients in primary care in Zambia.* BMC Psychiatry., 2011. **11:75**.(doi): p. 10.1186/1471-244X-11-75.
64. Myer, L., J. Smit, L.L. Roux, et al., *Common mental disorders among HIV-infected individuals in South Africa: prevalence, predictors, and validation of brief psychiatric rating scales.* AIDS Patient Care STDS., 2008. **22**(2): p. 147-58. doi: 10.1089/apc.2007.0102.
65. Natamba, B.K., J. Achan, A. Arbach, et al., *Reliability and validity of the center for epidemiologic studies-depression scale in screening for depression among HIV-infected and -uninfected pregnant women attending antenatal services in northern Uganda: a cross-sectional study.* BMC Psychiatry., 2014. **14:303**.(doi): p. 10.1186/s12888-014-0303-y.

66. Pedroza, C. and V.T. Thanh Truong, *Performance of models for estimating absolute risk difference in multicenter trials with binary outcome*. BMC Med Res Methodol., 2016. **16**(1): p. 113. doi: 10.1186/s12874-016-0217-0.
67. Zou, G., *A modified poisson regression approach to prospective studies with binary data*. Am J Epidemiol., 2004. **159**(7): p. 702-6.
68. Baron, R.M. and D.A. Kenny, *The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations*. J Pers Soc Psychol., 1986. **51**(6): p. 1173-82.
69. Perez, F., C. Zvandaziva, B. Engelsmann, et al., *Acceptability of routine HIV testing ("opt-out") in antenatal services in two rural districts of Zimbabwe*. J Acquir Immune Defic Syndr., 2006. **41**(4): p. 514-20.
70. Reddy, P., K. Zuma, O. Shisana, et al., *Prevalence of tobacco use among adults in South Africa: Results from the first South African National Health and Nutrition Examination Survey*. S Afr Med J, 2015. **105**(8): p. 648-55.
71. Peltzer, K., A. Davids, and P. Njuho, *Alcohol use and problem drinking in South Africa: findings from a national population-based survey*. Afr J Psychiatry, 2010. **14**: p. 30-37.
72. Koyanagi, A., B. Stubbs, and D. Vancampfort, *Correlates of sedentary behavior in the general population: A cross-sectional study using nationally representative data from six low- and middle-income countries*. PLoS One., 2018. **13**(8): p. e0202222. doi: 10.1371/journal.pone.0202222. eCollection 2018.
73. Bhana, A., S.D. Rathod, O. Selohilwe, et al., *Characteristics and correlates of alcohol consumption among adult chronic care patients in North West Province, South Africa*. S Afr Med J, 2017. **107**(7): p. 636-642.
74. Magidson, J.F., W. Saal, A. Nel, et al., *Relationship between depressive symptoms, alcohol use, and antiretroviral therapy adherence among HIV-infected, clinic-attending patients in South Africa*. J Health Psychol., 2017. **22**(11): p. 1426-1433. doi: 10.1177/1359105316628743. Epub 2016 Feb 15.
75. Duval, X., G. Baron, D. Garelik, et al., *Living with HIV, antiretroviral treatment experience and tobacco smoking: results from a multisite cross-sectional study*. Antivir Ther, 2008. **13**(3): p. 389-97.
76. Brath, H., I. Grabovac, H. Schalk, et al., *Prevalence and Correlates of Smoking and Readiness to Quit Smoking in People Living with HIV in Austria and Germany*. PLoS One, 2016. **11**(2): p. e0150553.

77. Lee, D.Y., E. Kim, and M.H. Choi, *Technical and clinical aspects of cortisol as a biochemical marker of chronic stress*. BMB Rep, 2015. **48**(4): p. 209-216.

### 3.8. Figures and Tables

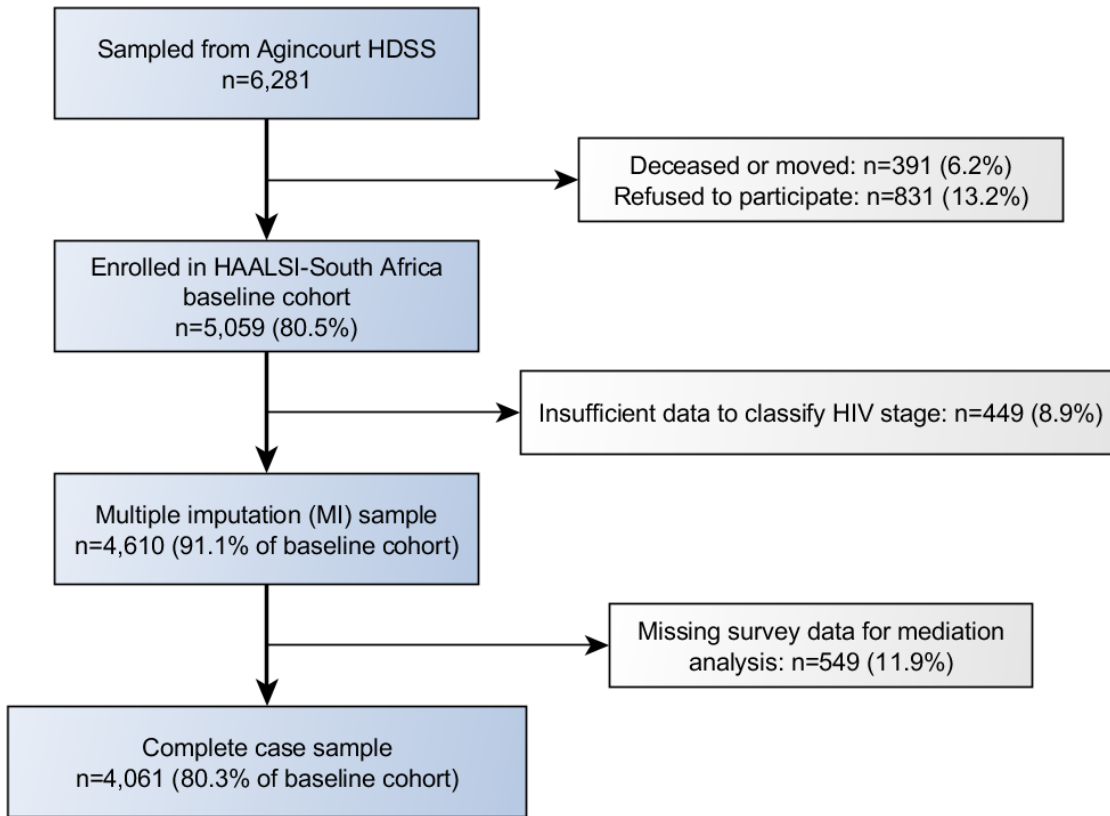
**Figure 3.1 Conceptual diagram of causal pathways between HIV continuum stage and CVD risk behaviors mediated by physiological and psychological symptoms**



78

*Note: Absence of an arrow from HIV+ unaware to psychological symptoms indicates no hypothesized mediation via psychological symptoms. Dashed lines indicate that symptom pathways are attenuated among individuals who are HIV+ on treatment. Arrows between physiological and psychological symptoms are omitted as the relationships between mediators were not tested in this study and assumed to have no effect.*

**Figure 3.2 Sample eligibility flowchart**



Note: Insufficient data to classify HIV continuum stage was primarily due to refusing consent to dried blood spot (DBS) testing (7%) or invalid DBS test data (3%)

**Table 3.1 Sample characteristics, adults aged 40 years and older residing in rural Agincourt district, South Africa, enrolled in HAALSI study, 2014-2015 (n=4,061)**

	Male, n=1,858	Female, n=2,203	Total, n=4,061
	n (%)	n (%)	n (%)
<b>Demographics</b>			
Age group			
40-49	325 (17%)	442 (20%)	767 (19%)
50-59	492 (26%)	685 (31%)	1,177 (29%)
60-69	543 (29%)	556 (25%)	1,099 (27%)
70+	498 (27%)	520 (24%)	1,018 (25%)
Completed primary education	424 (23%)	402 (18%)	826 (20%)
Employed (full or part-time)	358 (19%)	311 (14%)	669 (16%)
Married	1,289 (69%)	853 (39%)	2,142 (53%)
Poorest 40% <sup>1</sup>	737 (40%)	886 (40%)	1,623 (40%)
<b>HIV-related</b>			
HIV continuum stage			
HIV-	1,400 (75%)	1,638 (74%)	3,038 (75%)
HIV+ unaware	112 (6%)	163 (7%)	275 (7%)
HIV+ aware untreated	40 (2%)	53 (2%)	93 (2%)
HIV+ on treatment	306 (16%)	349 (16%)	655 (16%)
Virally suppressed (among HIV+)	231 (54%)	282 (53%)	513 (54%)
<b>CVD risk behaviors</b>			
Tobacco smoking <sup>2</sup>	364 (20%)	7 (<1%)	371 (9%)
Hazardous alcohol use <sup>3</sup>	290 (16%)	96 (4%)	386 (10%)
Sedentary behavior <sup>4</sup>	774 (42%)	957 (43%)	1,731 (43%)
<b>CVD history</b>			
Hypertension	650 (35%)	1,075 (49%)	1,725 (42%)
Dyslipidemia or heart disease	218 (12%)	295 (13%)	513 (13%)
Diabetes	118 (6%)	152 (7%)	270 (7%)
<b>Physiological symptoms</b>			
Muscle weakness	1,554 (84%)	1,106 (50%)	2,660 (66%)
Pain	131 (7%)	212 (10%)	343 (8%)
Cognitive difficulties (memory/concentration/learning)	737 (40%)	974 (44%)	1,711 (42%)
Physical dysfunction (difficulties with ADLs)	175 (9%)	178 (8%)	353 (9%)
<b>Psychological symptoms</b>			
Depressive symptoms (CESD-8 score 5+ out of 8)	124 (7%)	194 (9%)	318 (8%)
Low subjective well-being	528 (28%)	635 (29%)	1,163 (29%)

Abbreviations: ADL - Activities of daily living; CESD - Center for Epidemiological Studies Depression Scale;

HAALSI - Health and Aging in Africa: A Longitudinal Study of an INDEPTH Community in South Africa

<sup>1</sup> Based on household wealth index.

<sup>2</sup> Self-reported current use of smoking tobacco (cigarettes, cigars or pipes).

<sup>3</sup> AUDIT-C score >4 for men, >3 for women out of 7 total points.

<sup>4</sup> Does not meet criteria for minimal physical activity using IPAQ scoring.

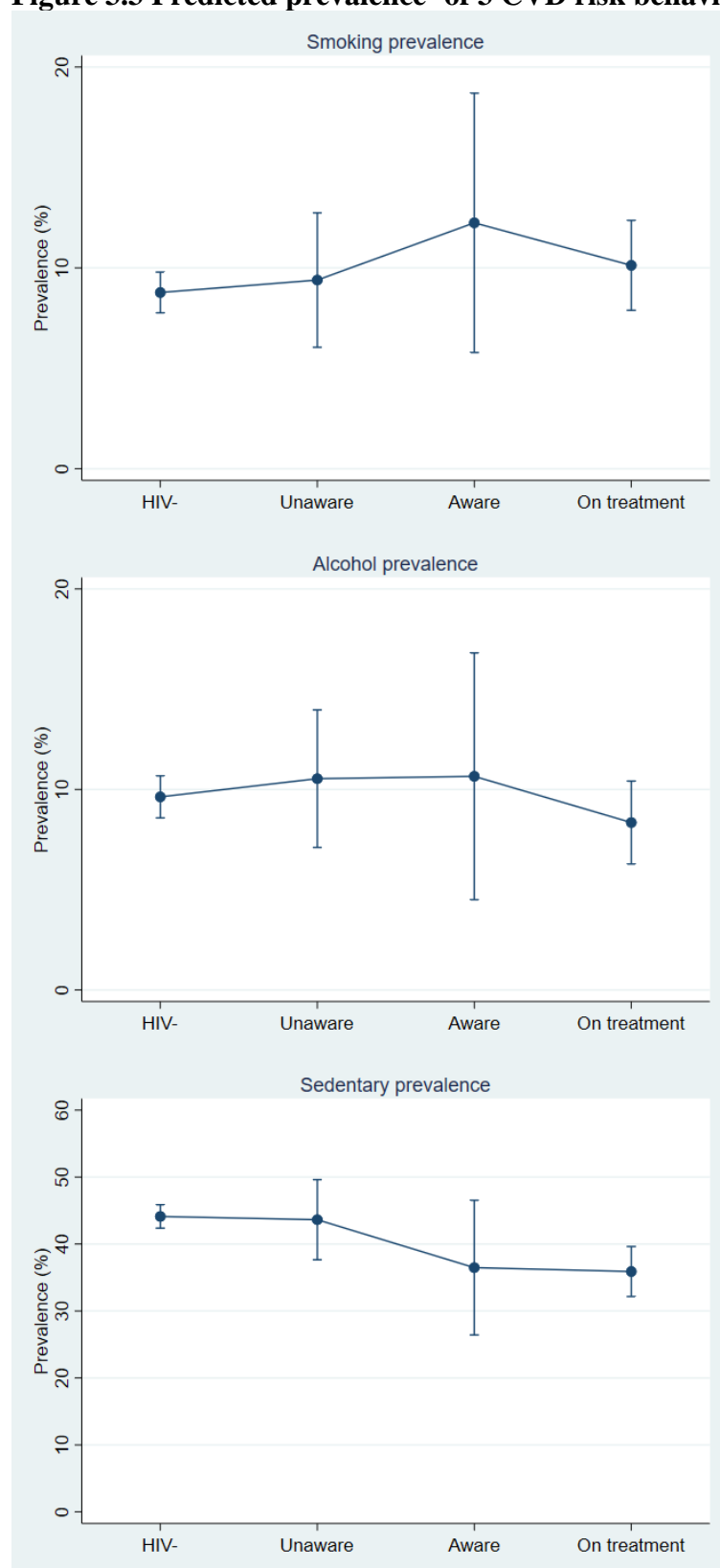
**Table 3.2 Prevalence ratios (PRs) for CVD risk behavior by HIV continuum stage, overall and by sex**

	Tobacco smoking		Hazardous alcohol use		Sedentary behavior	
	Unadjusted PR (95% CI)	Adjusted <sup>1</sup> PR (95% CI)	Unadjusted PR (95% CI)	Adjusted <sup>1</sup> PR (95% CI)	Unadjusted PR (95% CI)	Adjusted <sup>1</sup> PR (95% CI)
<b>Overall (n=4,061)</b>						
<b>HIV status</b>						
HIV-	reference	reference	reference	reference	reference	reference
HIV+ (all)	<b>1.25 (1.00, 1.55)</b>	1.15 (0.93, 1.43)	1.07 (0.86, 1.33)	1.01 (0.81, 1.25)	<b>0.84 (0.77, 0.92)</b>	<b>0.87 (0.80, 0.95)</b>
<b>HIV continuum stage</b>						
HIV-	reference	reference	reference	reference	reference	reference
HIV+ unaware	1.19 (0.82, 1.72)	1.07 (0.74, 1.56)	1.19 (0.84, 1.69)	1.09 (0.78, 1.54)	0.95 (0.82, 1.09)	0.99 (0.85, 1.14)
HIV+ aware untreated	1.50 (0.87, 2.58)	1.40 (0.81, 2.39)	1.13 (0.63, 2.06)	1.11 (0.61, 1.99)	0.80 (0.60, 1.05)	0.83 (0.63, 1.09)
HIV+ on treatment	1.24 (0.97, 1.60)	1.15 (0.90, 1.48)	0.92 (0.70, 1.20)	0.87 (0.66, 1.14)	<b>0.79 (0.70, 0.88)</b>	<b>0.81 (0.73, 0.91)</b>
<b>Males (n=1,858)</b>						
<b>HIV status</b>						
HIV-	reference	reference	reference	reference	reference	reference
HIV+ (all)	<b>1.28 (1.05, 1.57)</b>	1.21 (0.99, 1.49)	1.10 (0.86, 1.40)	1.05 (0.82, 1.33)	<b>0.84 (0.77, 0.92)</b>	0.89 (0.78, 1.02)
<b>HIV continuum stage</b>						
HIV-	reference	reference	reference	reference	reference	reference
HIV+ unaware	1.37 (0.90, 1.83)	1.24 (0.81, 1.67)	1.45 (0.92, 1.98)	1.31 (0.84, 1.77)	0.89 (0.67, 1.11)	0.94 (0.71, 1.16)
HIV+ aware untreated	1.64 (0.84, 2.44)	1.55 (0.81, 2.30)	0.97 (0.24, 1.70)	0.94 (0.24, 1.64)	0.81 (0.47, 1.16)	0.84 (0.48, 1.20)
HIV+ on treatment	1.22 (0.93, 1.50)	1.17 (0.90, 1.45)	0.91 (0.63, 1.19)	0.88 (0.62, 1.15)	<b>0.86 (0.72, 0.99)</b>	0.87 (0.73, 1.01)
<b>Females (n=2,203)<sup>2</sup></b>						
<b>HIV status</b>						
HIV-	reference	reference	reference	reference	reference	reference
HIV+ (all)	1.26 (0.24, 6.47)	1.27 (0.27, 5.92)	1.04 (0.67, 1.65)	1.02 (0.65, 1.60)	<b>0.82 (0.72, 0.92)</b>	<b>0.86 (0.75, 0.96)</b>
<b>HIV continuum stage</b>						
HIV-	reference	reference	reference	reference	reference	reference
HIV+ unaware	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.84 (0.15, 1.52)	0.82 (0.16, 1.48)	0.98 (0.80, 1.15)	1.02 (0.84, 1.20)
HIV+ aware untreated	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.72 (0.05, 3.38)	1.83 (0.13, 3.53)	0.78 (0.50, 1.07)	0.82 (0.52, 1.13)
HIV+ on treatment	1.88 (0.37, 9.64)	1.96 (0.41, 9.32)	0.91 (0.40, 1.42)	0.88 (0.38, 1.38)	<b>0.73 (0.61, 0.84)</b>	<b>0.76 (0.64, 0.88)</b>

<sup>1</sup> Prevalence ratios were calculated using log-Poisson regression and robust standard errors, adjusted for age, education (at least primary), employed (full or part-time), wealth index (poorest 40% vs. richest 60%), hypertension, dyslipidemia, diabetes and prior CVD. Bolded estimates are significant at  $\alpha < 0.05$ .

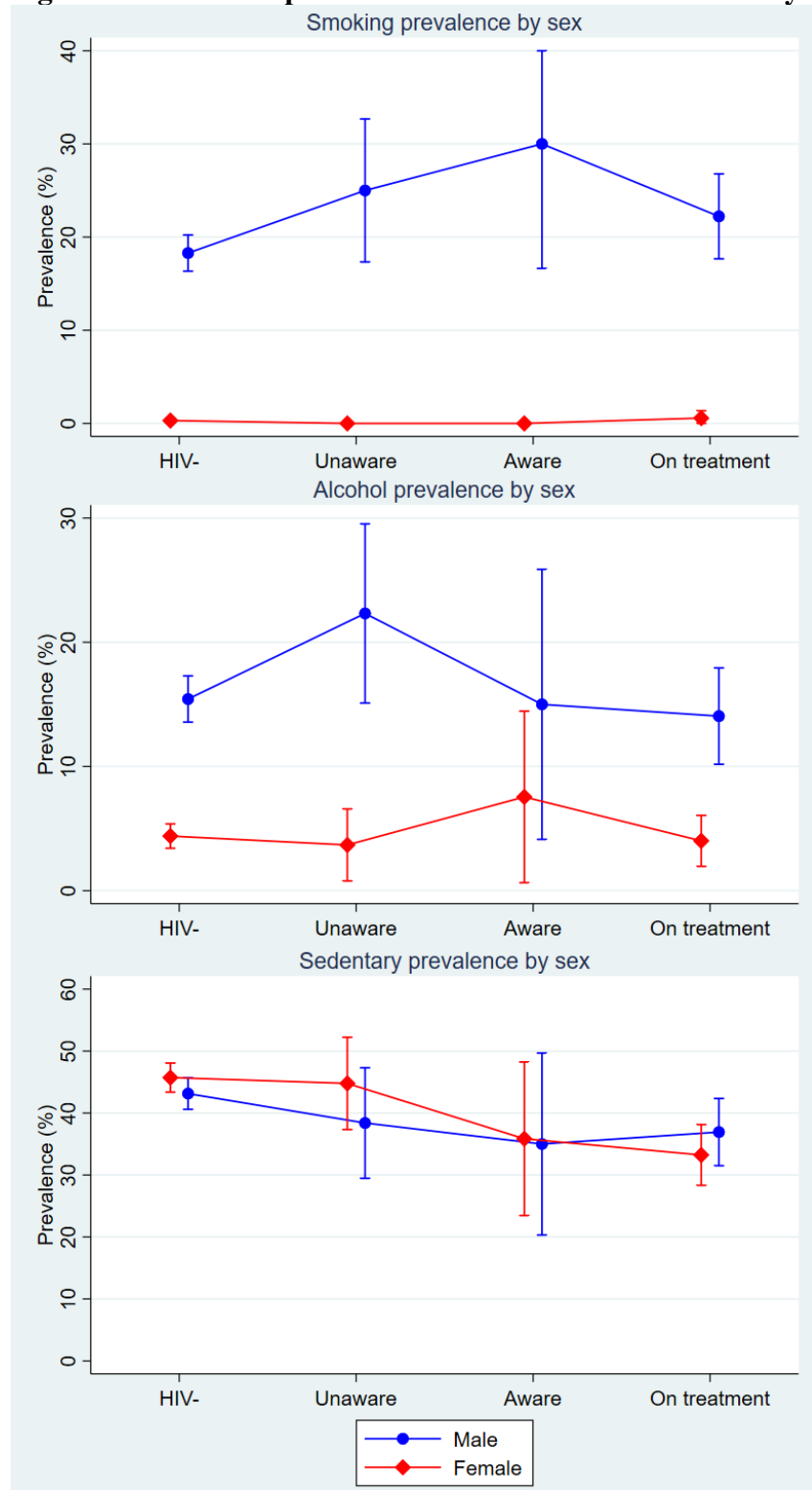
<sup>2</sup> Prevalence ratio estimates of 0 in the model for smoking among females were due to no reported cases of smoking.

**Figure 3.3 Predicted prevalence<sup>1</sup> of 3 CVD risk behaviors by HIV continuum stage**



<sup>1</sup> Predicted prevalences were estimated by log-Poisson regression models after adjustment for covariates.

**Figure 3.4 Predicted prevalence<sup>1</sup> of 3 CVD risk behaviors by HIV continuum stage and sex**



<sup>1</sup> Predicted prevalences were estimated by log-Poisson regression models after adjustment for covariates.

**Table 3.3 Prevalence (95% CI) of hypothesized mediators by HIV continuum stage and by outcome**

	Physiological symptoms				Psychological symptoms	
	Muscle weakness	Pain	Physical dysfunction	Cognitive impairment	Depressive symptoms	Low subjective well-being
	Prevalence <sup>1</sup> (95% CI)	Prevalence (95% CI)	Prevalence (95% CI)	Prevalence (95% CI)	Prevalence (95% CI)	Prevalence (95% CI)
<b>HIV continuum stage</b>						
HIV–	67% (66%, 69%)	9% (9%, 11%)	44% (42%, 46%)	9% (8%, 10%)	8% (7%, 9%)	28% (27%, 30%)
HIV+ unaware	58% (52%, 64%)	7% (5%, 11%)	34% (29%, 40%)	7% (4%, 11%)	7% (4%, 11%)	26% (21%, 31%)
HIV+ aware untreated	56% (46%, 66%)	4% (2%, 11%)	47% (37%, 57%)	9% (4%, 16%)	7% (3%, 14%)	31% (23%, 41%)
HIV+ on treatment	61% (57%, 65%)	5% (4%, 7%)	37% (34%, 41%)	7% (5%, 9%)	7% (5%, 9%)	30% (27%, 34%)
<b>Smoking</b>						
No	64% (62%, 65%)	9% (8%, 10%)	43% (42%, 45%)	9% (8%, 10%)	8% (7%, 9%)	29% (27%, 30%)
Yes	85% (81%, 88%)	7% (5%, 10%)	31% (27%, 36%)	9% (6%, 12%)	5% (3%, 8%)	27% (23%, 32%)
<b>Hazardous alcohol use</b>						
No	64% (63%, 66%)	9% (8%, 10%)	43% (41%, 44%)	9% (8%, 10%)	8% (7%, 9%)	28% (27%, 30%)
Yes	77% (73%, 81%)	7% (4%, 9%)	39% (34%, 44%)	10% (7%, 13%)	6% (4%, 9%)	35% (30%, 39%)
<b>Sedentary behavior</b>						
No	63% (61%, 65%)	6% (5%, 7%)	40% (38%, 42%)	6% (5%, 7%)	7% (6%, 8%)	27% (25%, 29%)
Yes	69% (67%, 71%)	11% (10%, 13%)	45% (42%, 47%)	12% (11%, 14%)	9% (7%, 10%)	31% (29%, 33%)

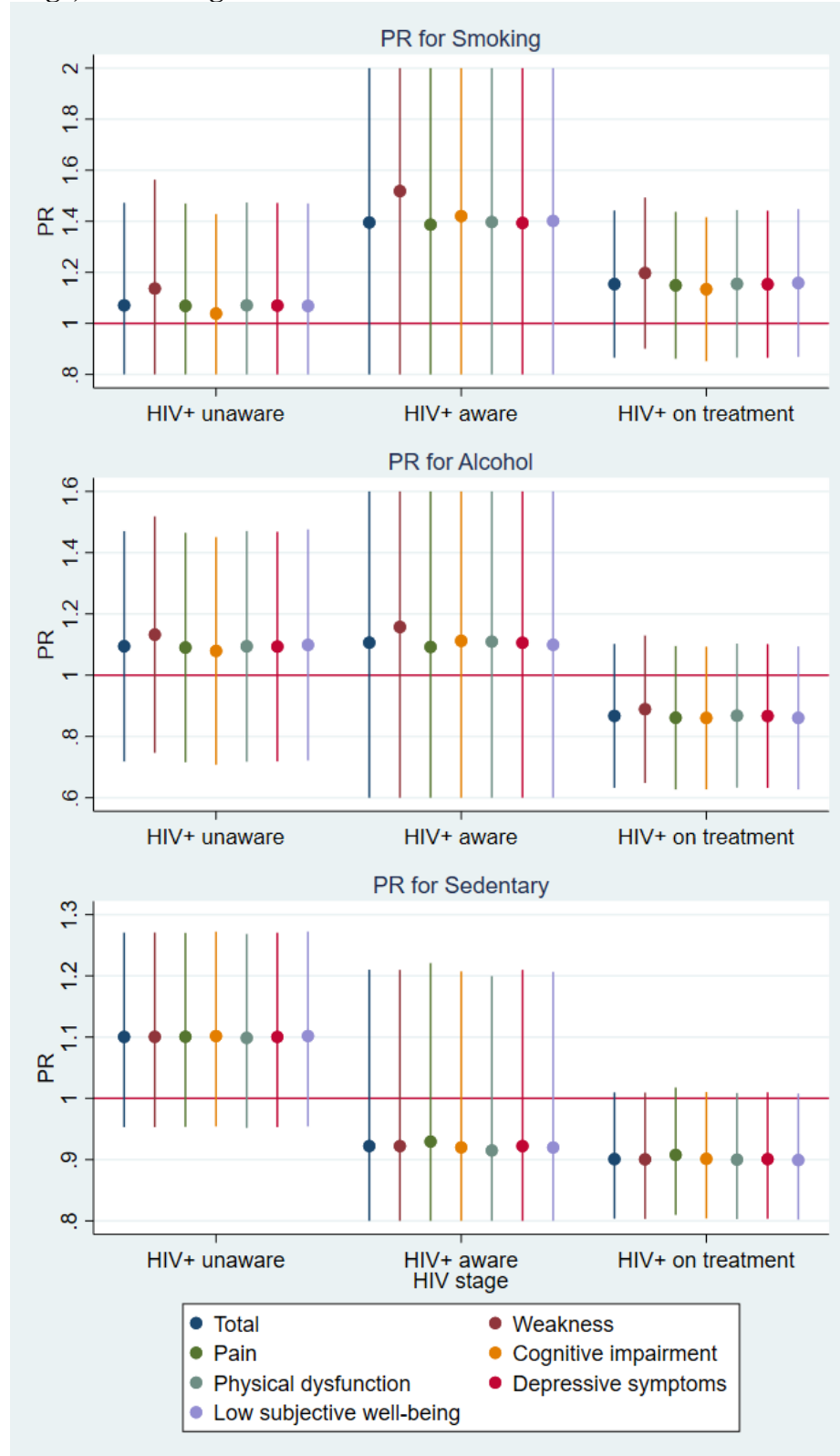
<sup>1</sup> Prevalence estimates are unadjusted.

**Table 3.4 Adjusted prevalence ratios (PRs) for CVD risk behavior by HIV continuum stage, controlling for individual mediators**

CVD risk behavior	Total effect	Direct effect, after controlling for					
		Physiological symptoms				Psychological symptoms	
		Muscle weakness	Pain	Physical dysfunction	Cognitive impairment	Depressive symptoms	Low subjective well-being
HIV continuum stage	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)
<b>Tobacco smoking</b>							
HIV–	reference	reference	reference	reference	reference	reference	reference
HIV+ unaware	1.07 (0.67, 1.47)	1.14 (0.71, 1.56)	1.07 (0.67, 1.47)	1.07 (0.67, 1.47)	1.04 (0.65, 1.43)	1.07 (0.67, 1.47)	1.07 (0.67, 1.47)
HIV+ aware untreated	1.40 (0.64, 2.15)	1.52 (0.72, 2.32)	1.39 (0.64, 2.14)	1.40 (0.64, 2.15)	1.42 (0.66, 2.19)	1.39 (0.63, 2.15)	1.40 (0.64, 2.16)
HIV+ on treatment	1.15 (0.87, 1.44)	1.20 (0.90, 1.49)	1.15 (0.86, 1.44)	1.15 (0.87, 1.44)	1.13 (0.85, 1.42)	1.15 (0.86, 1.44)	1.16 (0.87, 1.45)
<b>Hazardous alcohol use</b>							
HIV–	reference	reference	reference	reference	reference	reference	reference
HIV+ unaware	1.09 (0.72, 1.47)	1.13 (0.75, 1.52)	1.09 (0.72, 1.46)	1.09 (0.72, 1.47)	1.08 (0.71, 1.45)	1.09 (0.72, 1.47)	1.10 (0.72, 1.48)
HIV+ aware untreated	1.11 (0.46, 1.76)	1.16 (0.48, 1.83)	1.09 (0.45, 1.73)	1.11 (0.46, 1.76)	1.11 (0.45, 1.77)	1.11 (0.46, 1.76)	1.10 (0.45, 1.75)
HIV+ on treatment	0.87 (0.63, 1.10)	0.89 (0.65, 1.13)	0.86 (0.63, 1.10)	0.87 (0.63, 1.10)	0.86 (0.63, 1.09)	0.87 (0.63, 1.10)	0.86 (0.63, 1.09)
<b>Sedentary behavior</b>							
HIV–	reference	reference	reference	reference	reference	reference	reference
HIV+ unaware	0.99 (0.85, 1.13)	1.00 (0.85, 1.14)	0.99 (0.85, 1.14)	1.00 (0.85, 1.14)	0.99 (0.85, 1.14)	0.99 (0.85, 1.13)	0.99 (0.85, 1.13)
HIV+ aware untreated	0.83 (0.60, 1.06)	0.83 (0.60, 1.07)	0.84 (0.60, 1.07)	0.83 (0.60, 1.06)	0.82 (0.59, 1.05)	0.83 (0.60, 1.06)	0.82 (0.60, 1.05)
HIV+ on treatment	0.81 (0.72, 0.90)	0.82 (0.73, 0.91)	0.82 (0.73, 0.92)	0.82 (0.73, 0.91)	0.82 (0.73, 0.91)	0.81 (0.72, 0.90)	0.81 (0.72, 0.90)

<sup>1</sup> Prevalence ratios were calculated using log-Poisson regression and robust standard errors, adjusted for age, education (at least primary), employed (full or part-time), married, poorest 40%, hypertension, dyslipidemia, and diabetes.

**Figure 3.5 Forest plot of prevalence ratios for CVD risk behaviors by HIV continuum stage, controlling for mediators**



**Table 3.5 Comparison of complete case analysis and MI regression model results**

	Main analysis among complete cases <sup>1</sup> (n=4,061)	MI analysis <sup>2</sup> (n=4,610)
CVD risk behavior	Adjusted PR <sup>3</sup> (95% CI)	Adjusted PR <sup>3</sup> (95% CI)
HIV continuum stage		
<b>Tobacco smoking</b>		
HIV–	reference	reference
HIV+ unaware	1.07 (0.74, 1.56)	1.02 (0.71, 1.47)
HIV+ aware untreated	1.40 (0.81, 2.39)	1.42 (0.81, 2.49)
HIV+ on treatment	1.15 (0.90, 1.48)	1.12 (0.88, 1.43)
<b>Hazardous alcohol use</b>		
HIV–	reference	reference
HIV+ unaware	1.09 (0.78, 1.54)	1.03 (0.74, 1.44)
HIV+ aware untreated	1.11 (0.61, 1.99)	1.24 (0.70, 2.20)
HIV+ on treatment	0.87 (0.66, 1.14)	0.89 (0.69, 1.14)
<b>Sedentary behavior</b>		
HIV–	reference	reference
HIV+ unaware	0.99 (0.85, 1.14)	0.96 (0.85, 1.10)
HIV+ aware untreated	0.83 (0.63, 1.09)	0.84 (0.64, 1.10)
HIV+ on treatment	<b>0.81 (0.73, 0.91)</b>	<b>0.82 (0.74, 0.91)</b>

<sup>1</sup> Prevalence ratios were calculated using log-Poisson regression and robust standard errors, adjusted for adjusted for age, education (at least primary), employed (full or part-time), married, poorest 40%, hypertension, dyslipidemia, and diabetes.

<sup>2</sup> Missing data was imputed for all variables except HIV continuum stage using chained equations with M=20 imputed datasets.

**Table 3.6 Sensitivity analyses for alternate exposure definitions**

<b>CVD risk behavior</b>	Main analysis <sup>1</sup>	Scenario 1 <sup>2</sup>	Scenario 2	Scenario 3
HIV continuum stage	Adjusted PR <sup>3</sup> (95% CI)	Adjusted PR <sup>3</sup> (95% CI)	Adjusted PR <sup>3</sup> (95% CI)	Adjusted PR <sup>3</sup> (95% CI)
<b>Tobacco smoking</b>				
HIV–	reference	reference	reference	reference
HIV+ unaware	1.07 (0.74, 1.56)	0.93 (0.54, 1.60)	1.07 (0.74, 1.56)	1.07 (0.74, 1.56)
HIV+ aware untreated	1.40 (0.81, 2.39)	1.30 (0.90, 1.89)	1.06 (0.46, 2.44)	1.40 (0.81, 2.39)
HIV+ on treatment	1.15 (0.90, 1.48)	1.15 (0.90, 1.48)	1.19 (0.94, 1.52)	1.29 (0.89, 1.89)
HIV+ virally suppressed				1.09 (0.80, 1.47)
<b>Hazardous alcohol use</b>				
HIV–	reference	reference	reference	reference
HIV+ unaware	1.09 (0.78, 1.54)	1.13 (0.72, 1.78)	1.09 (0.78, 1.54)	1.09 (0.78, 1.54)
HIV+ aware untreated	1.11 (0.61, 1.99)	1.07 (0.73, 1.58)	0.81 (0.32, 2.07)	1.11 (0.61, 1.99)
HIV+ on treatment	0.87 (0.66, 1.14)	0.87 (0.66, 1.13)	0.90 (0.70, 1.17)	0.79 (0.49, 1.26)
HIV+ virally suppressed				0.90 (0.66, 1.24)
<b>∞ Sedentary behavior</b>				
HIV–	reference	reference	reference	reference
HIV+ unaware	0.99 (0.85, 1.14)	0.99 (0.82, 1.19)	0.99 (0.86, 1.14)	0.99 (0.85, 1.14)
HIV+ aware untreated	0.83 (0.63, 1.09)	0.92 (0.78, 1.09)	0.86 (0.59, 1.24)	0.83 (0.63, 1.09)
HIV+ on treatment	<b>0.81 (0.73, 0.91)</b>	<b>0.81 (0.73, 0.91)</b>	<b>0.81 (0.73, 0.91)</b>	<b>0.81 (0.67, 0.98)</b>
HIV+ virally suppressed				<b>0.82 (0.72, 0.93)</b>

<sup>1</sup> Base case results represent the main adjusted model among both males and females.

<sup>2</sup> In scenario 1, “unaware” individuals were re-classified as “aware” if they reported being previously tested for HIV, had their last HIV test done at least 6 months ago and had a detectable viral load. In scenario 2, individuals who tested ART-negative but reported being on ART were re-classified as ART-positive. In scenario 3, “treated” individuals who had an undetectable viral load test were re-classified into a separate “virally suppressed” group.

<sup>3</sup> Prevalence ratios were calculated using log-Poisson regression and robust standard errors, adjusted for adjusted for age, education (at least primary), employed (full or part-time), married, poorest 40%, hypertension, dyslipidemia, and diabetes.

## CHAPTER 4. DOES PERCEIVED LIFE EXPECTANCY MODIFY THE EFFECTS OF HIV ON CVD RISK BEHAVIORS? A SELF-REGULATION HYPOTHESIS

### 4.1. Abstract

**Background:** Cardiovascular disease (CVD) risk behaviors are highly prevalent among people living with HIV (PLWH). Evidence suggests that HIV itself may influence CVD risk behaviors, making them a particularly important CVD prevention target in this population. Modifying CVD risk behaviors, however, has proven difficult for PLWH; identifying drivers of unhealthy behaviors is therefore crucial for designing effective interventions. Self-regulation theory postulates that health behaviors depend on individuals' beliefs about the health threats they expect to face in the future. Thus, perceived life expectancy (PLE) may be a relevant factor for health prevention behaviors, especially those that are related to age-related health conditions, such as CVD. We hypothesized that individuals with low PLE would be more prone to adopting unhealthy behaviors as a result of their HIV than those with high PLE. This study aimed to test the joint effects of HIV continuum stage and low PLE on CVD risk behaviors among older adults.

**Methods:** We conducted secondary analyses of baseline data from a population-based cohort study of adults 40 years and older in rural Agincourt district in South Africa. HIV continuum stage was assessed using biomarker data on HIV infection status, detectable ARVs and self-reported HIV status to construct four groups (HIV-negative, HIV-positive unaware, HIV-positive aware untreated, HIV-positive on treatment). Low PLE was defined as having <50% self-reported probability of survival to old age (between 80 and 100 years depending on the current age of the participant). These data were combined to construct a composite variable of HIV continuum stage and PLE. Outcomes were self-reported current smoking, hazardous alcohol use

and sedentary behavior.. Log-Poisson regression models were fit to assess the prevalence ratios (PR) of each CVD risk behavior across joint categories of HIV continuum stage and low vs. high PLE to assess whether effects of HIV continuum stage on each CVD risk behavior varied by PLE level.

**Results:** A total of n=3,232 participants were included in the study, among whom 10% were smokers, 10% were hazardous alcohol users and 41% were sedentary. Smoking was associated with HIV continuum stage only among those with low PLE. Compared to the HIV-negative and high PLE reference group, the highest prevalence of smoking was observed among the HIV-positive aware untreated and low PLE group: PR (95% CI) = 4.43 (1.79, 10.97). In contrast, no significant effects of HIV continuum stage or low PLE were observed for hazardous alcohol use, and protective effects were observed for sedentary behaviors, with the lowest prevalence of sedentary being observed in the HIV-positive on treatment and low PLE group: 0.55 (0.37, 0.83). Findings were minimally sensitive to missing data on PLE.

**Discussion:** The results of this study suggest that the effects of HIV continuum stage on smoking are stronger among individuals with low vs. high PLE. However, no such findings were noted with regards to hazardous alcohol use and sedentary behaviors. This study lends support to the self-regulation hypothesis for smoking in HIV-positive populations. Further research is necessary to explore why findings differed across health behaviors.

## 4.2. Introduction

People living with HIV (PLWH) experience higher rates of cardiovascular disease (CVD) than the general population.<sup>1-4</sup> This excess risk is due in part to elevated behavioral risk factors, such as tobacco smoking, hazardous alcohol use and sedentary behaviors.<sup>5-19</sup> As a result, behavioral modification interventions have increasingly been offered to PLWH. However, these interventions have been shown to be largely ineffective, with recent systematic reviews showing that the benefits of smoking and alcohol cessation interventions for PLWH dissipate within as little as 6 months after the end of the intervention.<sup>20, 21</sup> Although most individuals, upon receiving their HIV diagnosis, report renewed interest in making healthy behavior changes, only one-third successfully reduce their smoking and/or alcohol use and up to 10% may increase such behaviors instead.<sup>22, 23</sup> Qualitative evidence suggests that this is not due to lack of motivation. For example, focus groups among HIV-positive smokers found that participants often expressed the desire to quit smoking; however, many believed that they would die from their HIV infection before they suffered the consequences of smoking.<sup>24</sup> That is, intentions to stop unhealthy behaviors may be outweighed by competing concerns regarding the ultimate negative impact of HIV infection and the immediate pleasure derived from the behaviors themselves.<sup>25, 26</sup> These conflicting motivations can undermine efforts to improve health behaviors and potentially explain why behavior modification interventions have not proven effective for PLWH.

This hypothesis is consistent with the self-regulation model of illness, which provides a theoretical basis for why individuals respond in various ways when confronting a health threat such as HIV infection. Self-regulation theory postulates that an individual's health behaviors depend not only on the health threats they currently face, but also on those they expect to face in the future.<sup>27, 28</sup> A key feature is that individuals make predictions about their future and regulate

or modify their current behaviors in accordance with these predictions.<sup>29</sup> Therefore, perceived life expectancy (PLE), which captures an individual's self-rated probability of survival to old age when aging-related diseases would be of greatest concern, may influence their current and near-term CVD prevention behaviors. As per self-regulation theory, we hypothesize that individuals with low PLE would have lower incentive to avoid CVD risk behaviors if they do not believe that the negative consequences (i.e., CVD complications) will manifest during their lifetime.

Concepts from self-regulation theory have been used previously to explain various health behaviors in diverse patient populations, such as why lung cancer patients continue smoking after their diagnosis<sup>30</sup> and what factors contribute to treatment non-adherence among PLWH.<sup>31</sup> Though these studies did not explicitly describe PLE, they found that health behaviors were often worse among persons with greater symptom severity and poorer perceived prognosis (e.g., perceived likelihood of survival ).<sup>30-32</sup> Further, HIV-positive persons commonly hold the misconception that HIV is a “death sentence”, a belief that often persists even among those on treatment.<sup>32</sup> These observations suggest that PLE likely varies by HIV infection, awareness and treatment status. If low PLE does indeed modify the effects of HIV-positive status on CVD risk behaviors, then its modifying effect would also vary by infection, awareness and treatment status as well.<sup>33</sup> Specifically, we hypothesized that persons who have low versus high PLE would be more likely to engage in increased CVD risk behaviors based on changes in their health status as a result of becoming HIV-infected. Similarly, those who have low PLE would be more likely to increase their CVD risk behaviors after becoming aware of their status due to already heightened fears of mortality (in the absence of treatment). Finally, those who have low PLE would be more likely to reduce their behaviors after initiating HIV treatment based on the extent to which their illness improves or is anticipated to improve. Therefore, comparing the relationship between

HIV continuum stages and CVD risk behavior across PLE levels can help to unpack this potential relationship.

PLE is likely not static over the course of an individual's life. Thus, it may be useful to operationalize the concept of PLE as comprising two components: time-varying *state* and stable personality *trait*.<sup>34</sup> The *state* component captures how PLE changes in response to life circumstances, while the *trait* component captures the degree to which individuals have an innate tendency to be more optimistic or pessimistic about their own survival. The state-trait distinction highlights uncertainties regarding the temporal relationships between PLE and HIV; under this framework, HIV status would alter the *state* component but not the *trait* component. A conceptual diagram of the relationship between HIV continuum stage, low PLE and CVD risk behaviors is displayed in Figure 4.1.

The effects of HIV and PLE on CVD risk behaviors are of particular interest for older persons living with HIV, since CVD is strongly associated with age.<sup>35</sup> Furthermore, older individuals comprise a fast-growing segment of the HIV-positive population, due to longer survival of PLWH on antiretroviral treatment, as well as data that demonstrate that such older populations remain at high risk of HIV acquisition due to failure of HIV prevention services to focus on this group and lower condom use and HIV testing rates as compared to younger age groups.<sup>36-39</sup> This trend is especially notable in the sub-Saharan African (SSA) region, which has the highest burden of HIV in the world, which has experienced a substantial scale-up of access to HIV treatment, and which is undergoing drastic urbanization accompanied by associated increases in sedentary behaviors and diets higher in processed foods.<sup>40, 41</sup> Currently, most HIV research

focuses on adolescents and younger adults of reproductive age; thus further research on HIV and CVD risk behaviors in older adults in sub-Saharan Africa (SSA) is needed.

To address these knowledge gaps, we explored the relationship between HIV and PLE and three CVD risk behaviors among a population-based cohort of adults aged 40 years and over in rural Agincourt district in South Africa. As secondary objectives, we examined whether findings were sensitive to alternative definitions of PLE that distinguish state and trait components in different ways.

### **4.3. Methods**

#### ***4.3.1. Data source***

This analysis used baseline data from the HAALSI study, a cohort study of adults 40 years and older in rural Agincourt district in South Africa. A sex-stratified random sample of 6,281 adults living in Agincourt district was selected from the Agincourt Health and Demographic Surveillance System (HDSS) and invited to participate in the study. From this sample, a total of 5,059 individuals were enrolled in the baseline cohort. Participants completed a survey designed to gather detailed information on overall health and functioning, including several HIV- and CVD-related measures. Consenting participants also completed a physical examination and provided dried blood spot (DBS) samples for biomarker testing. Participants were eligible for this analysis if they had valid data on all variables used in the analysis as described below.

Survey instruments were translated from English to the local Shangaan language and administered by trained fieldworkers using electronic tablets. Recruitment and baseline data collection occurred from 2014 to 2015. The HAALSI study received ethical approvals from

Harvard School of Public Health, University of Witwatersrand in South Africa, and the Mpumalanga Provincial Research and Ethics Committee.

#### **4.3.2. Measures**

We constructed a categorical variable for HIV continuum stage, using a combination of DBS data on HIV infection and ART use status (detectable 3TC or FTC), and self-reported HIV status to create four categories: HIV-, HIV-positive unaware, HIV-positive aware untreated, and HIV-positive on treatment.

Three CVD risk behavior outcomes were defined using self-reported data. Smoking was defined as current use of tobacco products, including cigarettes, cigars or pipes. Hazardous alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT-C), a validated screening tool that elicits self-reported data on alcohol use frequency, severity and binge drinking. Out of a total of 12 possible points, we classified hazardous alcohol use using validated cut-points for men (>4) and women (>3), respectively.<sup>42, 43</sup> Sedentary behavior was assessed using the International Physical Activity Questionnaire (IPAQ). We categorized individuals who failed to meet criteria for minimum physical activity as having sedentary behaviors. See Appendix Tables 5.7 and 5.8 for detailed information on the survey questions used to operationalize hazardous alcohol use and sedentary behavior.

PLE was assessed using the question: “*What is the percent chance that you will live to be X or more*”, where *X* was an age between 80-100 chosen by the interviewer to be at least 10 years greater than the participant’s current age (median 25 years). Responses ranged from 0-100%. In

the absence of validated thresholds for this measure, we dichotomized low versus high PLE using a 50% cut-point.

Several demographic and health-related variables were considered potential confounders of the relationships between HIV continuum stage, PLE and CVD risk behaviors, including sex, age (continuous), employment status (full- or part-time employment vs. neither), education (completed at least primary education), poorest 40% (as measured by a composite wealth index, based on household assets).

A set of measures of HIV-related symptoms were also included as predictors of PLE for sensitivity analyses (see below). Muscle weakness was measured via hand grip strength tests and defined using validated clinical thresholds.<sup>44</sup> Pain was assessed using the Brief Pain Inventory (self-reported severity of pain experienced and degree to which pain interferes with life).<sup>45, 46</sup> Physical dysfunction was defined as having difficulties in performing any one of six activities of daily living using the validated Katz Index of Independence in ADLs. Cognitive impairment was defined as self-reported difficulties with memory, concentration and/or learning new tasks.

### **4.3.3. Analysis**

Sample characteristics were described using proportions for categorical data and measures of central tendency for continuous data. To assess whether PLE modified the effect of HIV on CVD risk behaviors, we ran log-Poisson regression models with robust standard errors including indicator variables for each combination of HIV status and high vs. low PLE. Prevalence ratios (PR) and 95% confidence intervals (CIs) for each CVD risk behavior were calculated for each category compared to the HIV-negative and high PLE reference group. To explore whether

effect estimates varied further by awareness and treatment status, we ran additional models using HIV continuum stage, including indicator variables further stratified by HIV continuum stage. In both sets of models, we examined the PRs to assess the joint effects of both exposures, and compared whether associations for a given HIV continuum stage on each CVD risk behavior differed by PLE level, with respect to magnitude and/or direction of association or statistical significance.<sup>47, 48</sup> Directed acyclic graphs (DAG) were constructed to identify potential confounders necessary for adjustment.<sup>49</sup>

#### **4.3.4. Sensitivity analyses**

Due to substantial missing data in the PLE variable (n=869, 22% of the available sample), we conducted a secondary analysis to assess potential selection bias. While most of these missing values resulted from “don’t know” responses, we hypothesized that individuals who do not report their PLE would have been more likely to smoke, drink or engage in sedentary behavior. We re-ran analyses assuming that all individuals with missing PLE in fact had low PLE and assessed how results changed.

As another sensitivity analysis, we created an alternative measure to isolate the *trait* component of PLE. We first hypothesized factors that might influence the time-varying *state* component of PLE. Linear regression was used to model PLE as a function of all hypothesized predictors for which data were available, including demographic characteristics (sex, age, education, employment status, and household wealth), CVD history (previously diagnosed hypertension, dyslipidemia, and diabetes), and HIV-related symptoms (muscle weakness, pain, physical dysfunction, and cognitive impairment). The aim of this model was to control for all variables that could theoretically influence a person’s self-reported PLE at the time of the survey, i.e., all

sources of variability in PLE other than intrinsic trait differences. Demographic characteristics capture variability by sex and age, which are known predictors of actual life expectancy, and socioeconomic status, which represent health-related resources such as nutrition and accessing care. Health characteristics such as CVD history and HIV-related symptoms capture known health issues that would likely influence one's perceived future health trajectory and consequently their likelihood of survival. Other potential predictors of PLE were tested but did not substantially change model results and were thus not included for parsimony (data not shown). The resulting model is represented by the following equation:

$$PLE_i = \beta_{0i} + \sum \beta_i Demographics + \sum \beta_i Health\ characteristics + \varepsilon_i$$

The resulting residual error term,  $\varepsilon_i$ , is the difference between an individual's observed and predicted PLE:  $\varepsilon_i = PLE_i - \widehat{PLE}_i$ . Linear regression implicitly treats this residual as a measurement of random or unexplained variability between the model's predicted PLE and each individual's observed PLE. Intuitively, it represents how different an individual's response is compared to others with the same profile of demographic and health characteristics (Figure 4.2). As a sensitivity analysis, we assumed that these residuals were not due to random variability but rather that the variability in PLE not explained by predictors of the *state* component of PLE captures the *trait* component. Residuals were therefore interpreted as a measure of an individual's intrinsic tendency to be more pessimistic or optimistic than others similar to them, under the strong assumption of no unmeasured predictors. Individuals with negative residuals were classified as having pessimistic traits, and those with positive residuals were classified as

having optimistic traits.<sup>4</sup> We re-ran the regression models using this alternative measure of PLE and examined whether findings were sensitive to this alternative measure. All analyses were performed using Stata v15.1 statistical software (College Station, Texas, USA).

## **4.4. Results**

### ***4.4.1. Sample characteristics***

After excluding observations with any missing data, our final analytic sample included n=3,232 participants, 64% of the entire cohort (Figure 4.3). The variables with the most missing data were PLE (23%) and HIV continuum stage (10%). Sample characteristics for the complete case sample are displayed in Table 4.1. Forty-seven percent were male, 49% were over age 60, and over 75% were poorly educated and unemployed. Overall, 837 (26%) were HIV-positive, of whom 225 (7%) were HIV+ unaware, 79 (2%) were HIV+ aware untreated and 533 (16%) were HIV-positive on treatment. The prevalence of current smoking, hazardous alcohol use and sedentary behaviors were 10%, 10% and 41%, respectively. The distribution of PLE was highly left-skewed, with a median of 80%. Only 473 (15%) participants were classified as having low (<50%) PLE as measured (Figure 4.4).

---

<sup>4</sup> In contrast to Chapter 3, HIV-related symptoms here includes physiological symptoms and excludes psychological symptoms. We hypothesized that psychological measures such as depressive symptoms also comprise state and trait components and that their trait components would be highly correlated with the trait component of PLE. Therefore, controlling for depressive symptoms would control the PLE trait component the model is attempting to extract.

#### 4.4.2. Regression models

Results from regression models are reported in Table 4.2. PRs for all CVD risk behaviors were null for all high PLE and HIV-positive groups compared to the high PLE and HIV-negative reference group, indicating no main effects for HIV continuum stage. In contrast, PRs for the low PLE and HIV-negative group compared to the high PLE and HIV-negative group were significant for smoking (PR [95% CI]: 1.43 [1.03, 1.97]) and sedentary behavior (0.77 [0.67, 0.89]); these findings suggest significant main effects of low PLE on elevated smoking and lower sedentary behaviors, and no main effects of PLE on hazardous alcohol use. Joint effects of HIV continuum stage and low PLE were stronger than low PLE alone for smoking and sedentary behavior. For these outcomes, joint effects varied across HIV continuum stage, with the highest smoking prevalence being observed among the HIV-positive aware untreated and low PLE group: adjusted PR (95% CI) = 3.09 (1.40, 6.83); however, differences between HIV continuum stages were not statistically significant (pairwise comparisons not shown). Hazardous alcohol use did not vary across categories of HIV continuum stage or PLE. In contrast, sedentary behaviors were lower among HIV-positive stage and low PLE groups relative to the HIV-negative and high PLE group, and did not vary by awareness or treatment status. These patterns are visually apparent in predicted prevalence charts displayed in Figure 4.5.

Of note, when comparing all HIV-positive versus HIV-negative individuals, HIV-positive status was significantly associated with lower sedentary behaviors in unadjusted analyses: PR (95% CI) = 0.87 (0.79, 0.97), but this association did not remain after adjustment for confounders: 0.97 (0.87, 1.08). HIV-positive status was not significantly associated with smoking or hazardous alcohol use in unadjusted or adjusted analyses. Low PLE alone, however, was associated with higher prevalence of smoking and lower prevalence of sedentary behaviors: adjusted PR (95%

CI) for smoking = 1.54 (1.13, 2.09), and for sedentary = 0.76 (0.65, 0.87). The joint effect of HIV-positive status and low PLE was stronger than low PLE alone for smoking: adjusted PR (95% CI) = 1.66 (1.10, 2.53), and sedentary behavior: 0.65 (0.47, 0.91).

#### **4.4.3. Sensitivity analyses**

**Trait component extraction.** Results from the trait extraction model are reported in Table 4.3. The demographic characteristics, traditional CVD risk factors and physiological HIV symptoms collectively explained 7.5% of the total variability in PLE. The strongest predictors were physical dysfunction: coefficient (95% CI) = -6.4 (-9.5, -3.2), and education: 3.3 (1.1, 5.5). The distribution of residuals was left-skewed and ranged between -74.9 to 39.9 (Figure 4.4). Of the 2,947 participants originally categorized as high PLE, n=884 (30%) were re-categorized as having a pessimistic PLE trait (Table 4.5). No participants were re-categorized in the opposite direction.

**Sensitivity analyses.** Models re-run using alternative definitions of PLE are displayed in Tables 4.6-4.8 for smoking, hazardous alcohol use, and sedentary behavior, respectively. In general, effects were attenuated in models where missing PLE values were re-classified as low PLE, due to CVD risk behaviors being less prevalent among the group with missing PLE than those who reported low PLE.

In contrast, models using the PLE trait component, are more similar to those using the original PLE measure. Pessimistic personality trait (i.e., low PLE trait component) was associated with increased smoking, though this finding was only marginally significant at the  $p < 0.10$  level: adjusted PR (95% CI) = 1.27 (0.99, 1.63). Pessimistic personality trait was also significantly

associated with lower sedentary behaviors: PR (95% CI) = 0.82 (0.75, 0.91). Smoking was highest in the HIV-positive aware untreated and pessimistic trait group: PR (95% CI) = 2.65 (1.49, 4.72). However, the significant effects found for the low PLE and HIV-negative and low PLE and HIV-positive on treatment groups in the original model were no longer significant in the PLE trait component model. Predicted prevalence estimates are displayed graphically in Figures 4.6-4.8. As in the main analyses, no clear patterns emerged for the optimistic trait group.

#### **4.5. Discussion**

In this study, we explored the relationships between HIV continuum stage, PLE, and smoking, hazardous alcohol use and sedentary behaviors in a population-based sample of older adults in South Africa. This study built upon prior research that shows that HIV continuum stage and PLE are independent risk factors for unhealthy behavior engagement. Results indicated that self-reported CVD risk behaviors were common in this setting. The high prevalence of CVD risk behaviors we observed was similar to estimates from previous studies in Southern Africa. For example, the first South Africa National Health and Nutrition Examination Survey (SA NHANES) estimated the national smoking prevalence to be 15%, and the South African National HIV, Incidence, Behaviour and Communication (SABSSM) 2008 survey estimated the national prevalence of hazardous alcohol use to be 9%.<sup>50,51</sup> Data from the Global Ageing and Adult Health (SAGE) survey in South Africa estimated sedentary behavior prevalence of 42% among adults 18 years or older, using the Global Physical Activity Questionnaire.<sup>52</sup>

We tested the hypothesis that PLE played a modifying role on the relationship between HIV and unhealthy behavior engagement as predicted by self-regulation theory. To this end, we examined the joint effects of HIV continuum stage and PLE on each outcome. We found significant main

effects of low PLE on smoking (higher risk) and sedentary behaviors (lower risk) and non-significant effects on hazardous alcohol use (higher risk). These findings provide evidence that low PLE may be an independent predictor of some CVD risk behaviors in this population, but evidence was inconsistent across outcomes. We did not find main effects of HIV-positive status on any of the three CVD risk behaviors. However, non-significant differences in smoking prevalence were found when stratified further by awareness and treatment status in the low PLE group. Specifically, smoking was 1.4 times as common among low PLE and HIV-negative individuals as compared to the high PLE and HIV-negative reference group; the highest prevalence was among the low PLE and HIV-positive aware untreated group, which had three-fold higher smoking prevalence than the high PLE and HIV-negative group. No significant effects were observed across the HIV continuum among those with high PLE. Our findings differ from previous studies which suggest that HIV-positive status is associated with increased smoking and alcohol use,<sup>25, 53-55</sup> while supporting the hypothesis that individuals who are HIV-positive and believe they have low probability of survival are more likely to smoke. In other words, our findings are consistent with the hypothesis that individuals who are HIV-positive and have low PLE would have the highest prevalence of smoking, which would be expected if they were causal partners of smoking. No prior studies to our knowledge have assessed the relationship between PLE and CVD risk behaviors.

Our findings suggested that low PLE is an independent predictor of smoking, which may explain why some individuals do not change smoking behaviors after HIV infection. However, the fact that findings were inconsistent across outcomes is cause for skepticism. We observed no significant main or interaction effects of low PLE on hazardous alcohol use, and found protective main and interaction effects of low PLE on sedentary behaviors. It may be possible that the

effects of low PLE vary across health behaviors, as smoking is more generally recognized as harmful than alcohol use or sedentary behaviors.<sup>56</sup> However, we cannot rule out reverse causation or the possibility that the available self-reported measures failed to properly capture the underlying constructs, potentially inducing spurious findings. Of note, the protective effects observed for sedentary behavior run counter to our hypothesis. This likely reflects poor construct validity, as our measure of sedentary behavior included non-recreational physical activity, which would be associated with manual labor, characteristic of low socioeconomic status (SES) work. If HIV risk were higher among individuals with lower SES, this could explain the low prevalence of sedentary behaviors among all HIV-positive stage groups; the relationships between SES and HIV risk has proven to be complex, however.<sup>57</sup> Furthermore, the high degree of missing data on PLE reflected a large number of “don’t know” responses, suggesting that participants may have had difficulty with comprehension or were unwilling to answer. Missing responses may have been more likely among individuals with low PLE and unhealthy behaviors, resulting in selection bias. Findings from our sensitivity analysis suggested that while results were attenuated, they were not very sensitive to missing data, and whether missing responses were truly more likely to be from individuals with low PLE remains speculation.

Our study had several limitations. Due to small sample sizes, we were underpowered to detect small associations, particularly in the HIV-positive unaware group (n=79). Nonetheless, we observed strongest effects in the HIV-positive aware untreated and low PLE group for smoking, which we hypothesized a priori would be the most susceptible group. Perhaps more importantly, the cross-sectional nature of the data hindered our ability to identify the directional relationships between HIV continuum stage, PLE, and CVD risk behaviors. Studies of behavioral outcomes

are especially susceptible to this limitation as it is well-known in the psychological literature that there is high inter-individual variability in behavioral responses to health-related stress.<sup>29</sup>

This concern partly motivated the trait component analysis. By isolating the trait component of PLE, we aimed to remove sources of variability that could have occurred after becoming infected, diagnosed or treated for HIV. Effect estimates held when using the trait component instead of PLE as measured, except in the models for smoking; nonetheless, while findings for smoking no longer remained significant, prevalence estimates followed similar patterns, suggesting that findings were not highly sensitive. However, little variability (7%) was collectively explained by the set of predictors included in the trait extraction model, and few participants were re-classified using the new measure overall. While it is theoretically possible that over 90% of the variability in PLE is truly determined by intrinsic personality traits, the absence of model specification errors is a strong and untestable assumption. Notably, we cannot rule out the existence of important unmeasured predictors of PLE, e.g., family health history, access to health care and social supports from family or caregivers. The use of linear regression was also likely an oversimplification of the relationship between PLE and its predictors. More importantly, existing research on the state-trait distinction utilizes repeated measures, hypothesizing that differences observed across time in the same individual capture state components and similarities across time capture trait components, the so-called latent state-trait approach.<sup>58</sup> In the absence of repeated measures, we adapted this approach to cross-sectional data, which relied on the stronger assumption that different individuals would be comparable after controlling for other measured predictors of PLE.

Strengths of this study include the large population-based sample which ensured representation across the HIV care continuum, as opposed to clinic-based samples or external general population comparison groups typically employed by other studies. In addition, the restriction of the sample to older adults yielded novel findings in an under-studied population that is especially prone to CVD risk. The older age distribution of our sample also likely strengthened our ability to detect any effects of PLE.

#### **4.6. Conclusion**

In conclusion, our study found that PLE was a strong independent predictor for smoking, but not for hazardous alcohol use or sedentary behaviors. Relationships between HIV continuum stage and CVD risk behaviors differed by PLE, with the strongest associations observed among the low PLE group. Our results suggest that screening and counseling for additional smoking cessation resources could be targeted towards persons with low PLE. However, further research, especially with prospective follow-up, is necessary to confirm these findings and unpack the reasons for lack of or opposite findings for hazardous alcohol use or sedentary behaviors, which may impact intervention development.

#### 4.7. References

1. Sackoff, J.E., D.B. Hanna, M.R. Pfeiffer, et al., *Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City*. *Ann Intern Med*, 2006. **145**(6): p. 397-406.
2. Clark, S.J., F.X. Gomez-Olive, B. Houle, et al., *Cardiometabolic disease risk and HIV status in rural South Africa: establishing a baseline*. *BMC Public Health*, 2015. **15**:135.(doi): p. 10.1186/s12889-015-1467-1.
3. Wada, N., L.P. Jacobson, M. Cohen, et al., *Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome-negative individuals followed simultaneously in long-term cohort studies, 1984-2008*. *Am J Epidemiol*, 2013. **177**(2): p. 116-25.
4. Hanna, D.B., C. Ramaswamy, R.C. Kaplan, et al., *Trends in Cardiovascular Disease Mortality Among Persons With HIV in New York City, 2001-2012*. *Clin Infect Dis*, 2016. **63**(8): p. 1122-1129.
5. Glass, T.R., C. Ungsedhapand, M. Wolbers, et al., *Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study*. *HIV Med*, 2006. **7**(6): p. 404-10.
6. Tesoriero, J.M., S.M. Gieryic, A. Carrascal, et al., *Smoking among HIV positive New Yorkers: prevalence, frequency, and opportunities for cessation*. *AIDS Behav*, 2010. **14**(4): p. 824-35.
7. Lifson, A.R. and H.A. Lando, *Smoking and HIV: prevalence, health risks, and cessation strategies*. *Curr HIV/AIDS Rep*, 2012. **9**(3): p. 223-30.
8. Mdodo, R., E.L. Frazier, S.R. Dube, et al., *Cigarette smoking prevalence among adults with HIV compared with the general adult population in the United States: cross-sectional surveys*. *Ann Intern Med*, 2015. **162**(5): p. 335-44.
9. Kelso, N.E., D.S. Sheps, and R.L. Cook, *The association between alcohol use and cardiovascular disease among people living with HIV: a systematic review*. *Am J Drug Alcohol Abuse*, 2015. **41**(6): p. 479-88.
10. Weinberger, A.H., P.H. Smith, A.P. Funk, et al., *Sex Differences in Tobacco Use Among Persons Living With HIV/AIDS: A Systematic Review and Meta-Analysis*. *J Acquir Immune Defic Syndr*, 2017. **74**(4): p. 439-453. doi: 10.1097/QAI.0000000000001279.

11. Shiau, S., S.M. Arpadi, M.T. Yin, et al., *Patterns of drug use and HIV infection among adults in a nationally representative sample*. *Addict Behav.*, 2017. **68:39-44**.(doi): p. 10.1016/j.addbeh.2017.01.015. Epub 2017 Jan 7.
12. Crane, H.M., M.E. McCaul, G. Chander, et al., *Prevalence and Factors Associated with Hazardous Alcohol Use Among Persons Living with HIV Across the US in the Current Era of Antiretroviral Treatment*. *AIDS Behav*, 2017. **11**(10): p. 017-1740.
13. Ikeda, M.L., N.T. Barcellos, P.R. Alencastro, et al., *Alcohol Drinking Pattern: A Comparison between HIV-Infected Patients and Individuals from the General Population*. *PLoS One.*, 2016. **11**(6): p. e0158535. doi: 10.1371/journal.pone.0158535. eCollection 2016.
14. Fisher, J.C., H. Bang, and S.H. Kapiga, *The association between HIV infection and alcohol use: a systematic review and meta-analysis of African studies*. *Sex Transm Dis*, 2007. **34**(11): p. 856-63.
15. Galvan, F.H., E.G. Bing, J.A. Fleishman, et al., *The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study*. *J Stud Alcohol.*, 2002. **63**(2): p. 179-86.
16. Joy, T., H.M. Keogh, C. Hadigan, et al., *Dietary fat intake and relationship to serum lipid levels in HIV-infected patients with metabolic abnormalities in the HAART era*. *AIDS.*, 2007. **21**(12): p. 1591-600. doi: 10.1097/QAD.0b013e32823644ff.
17. Schafer, J., J. Young, A. Calmy, et al., *High prevalence of physical inactivity among patients from the Swiss HIV Cohort Study*. *AIDS Care.*, 2017. **29**(8): p. 1056-1061. doi: 10.1080/09540121.2016.1274016. Epub 2017 Jan 5.
18. Schuelter-Trevisol, F., F.H. Wolff, P.R. Alencastro, et al., *Physical activity: do patients infected with HIV practice? How much? A systematic review*. *Curr HIV Res.*, 2012. **10**(6): p. 487-97.
19. Mdege, N.D., S. Shah, O.A. Ayo-Yusuf, et al., *Tobacco use among people living with HIV: analysis of data from Demographic and Health Surveys from 28 low-income and middle-income countries*. *Lancet Glob Health.*, 2017. **5**(6): p. e578-e592. doi: 10.1016/S2214-109X(17)30170-5.
20. Pool, E.R., O. Dogar, R.P. Lindsay, et al., *Interventions for tobacco use cessation in people living with HIV and AIDS*. *Cochrane Database Syst Rev.*, 2016(6): p. CD011120. doi: 10.1002/14651858.CD011120.pub2.

21. Scott-Sheldon, L.A.J., K.B. Carey, B.T. Johnson, et al., *Behavioral Interventions Targeting Alcohol Use Among People Living with HIV/AIDS: A Systematic Review and Meta-Analysis*. *AIDS Behav.*, 2017. **21**(Suppl 2): p. 126-143. doi: 10.1007/s10461-017-1886-3.
22. Wang, Y., X. Chen, X. Li, et al., *Cigarette smoking among Chinese PLWHA: An exploration of changes in smoking after being tested HIV positive*. *AIDS Care*, 2016. **28**(3): p. 365-9.
23. Wang, Y., X. Chen, J. Ball, et al., *Self-reported changes in alcohol use behavior among people living with HIV in China after receiving HIV positive diagnosis*. *SAGE Open Med.*, 2018. **6**:2050312118755783.(doi): p. 10.1177/2050312118755783. eCollection 2018.
24. Reynolds, N.R., J.L. Neidig, and M.E. Wewers, *Illness representation and smoking behavior: a focus group study of HIV-positive men*. *J Assoc Nurses AIDS Care.*, 2004. **15**(4): p. 37-47.
25. Reynolds, N.R., *Cigarette smoking and HIV: more evidence for action*. *AIDS Educ Prev.*, 2009. **21**(3 Suppl): p. 106-21. doi: 10.1521/aeap.2009.21.3\_suppl.106.
26. Shuter, J., S.L. Bernstein, and A.B. Moadel, *Cigarette smoking behaviors and beliefs in persons living with HIV/AIDS*. *Am J Health Behav.*, 2012. **36**(1): p. 75-85.
27. Leventhal, H., I. Brissette, E.A. Leventhal, et al., *The common sense model of self-regulation of health and illness*, in *The Self-Regulation of Health and Illness Behavior*. 2003, Routledge: London. p. 42-65.
28. Leventhal, H., Y. Benyamini, S. Brownlee, et al., *Illness representations and coping with health threats*, in *Handbook of psychology and health*, A. Baum, S.E. Taylor, and J.E. Singer, Editors. 1997, Lawrence Erlbaum: Hillsdale, NJ.
29. Diefenebach, M.A. and H. Leventhal, *The common-sense model of illness representation: Theoretical and practical considerations*. *Journal of Social Distress and the Homeless*, 1996. **5**: p. 11-38.
30. Browning, K.K., M.E. Wewers, A.K. Ferketich, et al., *The Self-regulation Model of Illness applied to smoking behavior in lung cancer*. *Cancer Nurs.*, 2009. **32**(4): p. E15-25. doi: 10.1097/NCC.0b013e3181a0238f.
31. Reynolds, N.R., *The problem of antiretroviral adherence: a self-regulatory model for intervention*. *AIDS Care.*, 2003. **15**(1): p. 117-24. doi: 10.1080/0954012021000039815.

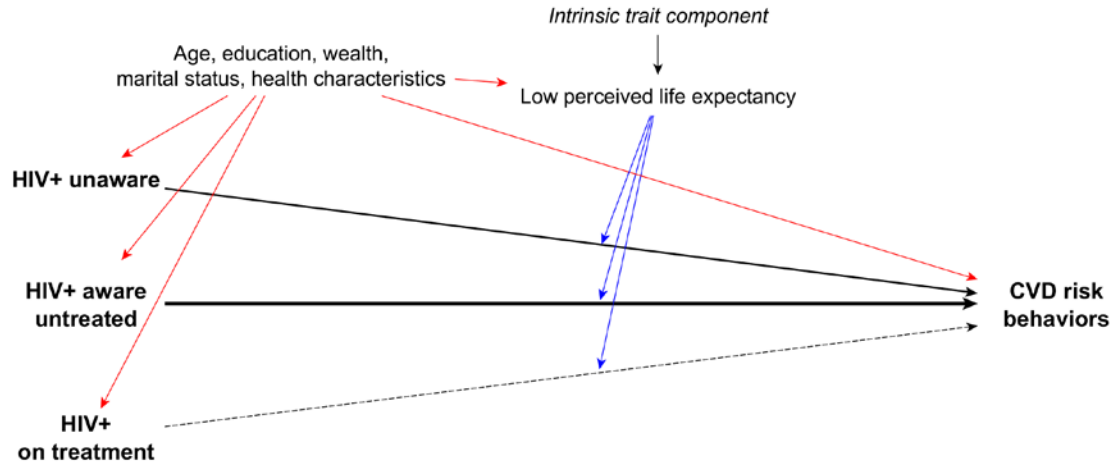
32. Terblanche, L.M. and E.L. Stellenberg, *Patient knowledge of HIV and its treatment in South Africa*. Afr J Prim Health Care Fam Med., 2014. **6**(1): p. E1-7. doi: 10.4102/phcfm.v6i1.518.
33. Vidrine, D.J., F.E. Fletcher, M.K. Buchberg, et al., *The influence of HIV disease events/stages on smoking attitudes and behaviors: project STATE (Study of Tobacco Attitudes and Teachable Events)*. BMC Public Health, 2014. **14**: p. 149.
34. Ferguson, E., *Personality is of central concern to understand health: towards a theoretical model for health psychology*. Health Psychol Rev, 2013. **7**(Suppl 1): p. S32-s70.
35. Vollmer, S., K. Harttgen, T. Alfven, et al., *The HIV Epidemic in Sub-Saharan Africa is Aging: Evidence from the Demographic and Health Surveys in Sub-Saharan Africa*. AIDS Behav, 2016.
36. Johnson, L.F., T.M. Rehle, S. Jooste, et al., *Rates of HIV testing and diagnosis in South Africa: successes and challenges*. AIDS., 2015. **29**(11): p. 1401-9. doi: 10.1097/QAD.0000000000000721.
37. Negin, J., B. Nemser, R. Cumming, et al., *HIV attitudes, awareness and testing among older adults in Africa*. AIDS Behav., 2012. **16**(1): p. 63-8. doi: 10.1007/s10461-011-9994-y.
38. Vollmer, S., T. Alfven, J. Padayachy, et al., *HIV surveys in older adults: better data, better health*. Lancet HIV., 2015. **2**(2): p. e40-1. doi: 10.1016/S2352-3018(15)00004-1. Epub 2015 Jan 29.
39. Rosenberg, M.S., F.X. Gomez-Olive, J.K. Rohr, et al., *Sexual Behaviors and HIV Status: A Population-Based Study Among Older Adults in Rural South Africa*. J Acquir Immune Defic Syndr., 2017. **74**(1): p. e9-e17.
40. UNAIDS, *Global report: UNAIDS report on the global AIDS epidemic 2013*. 2013: Geneva, Switzerland.
41. Bain, L.E., A.P. Kum, N.C. Ekukwe, et al., *HIV, cardiovascular disease, and stroke in sub-Saharan Africa*. Lancet HIV, 2016. **3**(8): p. e341-2.
42. Seth, P., M. Glenshaw, J.H. Sabatier, et al., *AUDIT, AUDIT-C, and AUDIT-3: drinking patterns and screening for harmful, hazardous and dependent drinking in Katutura, Namibia*. PLoS One, 2015. **10**(3): p. e0120850.

43. Bush, K., D.R. Kivlahan, M.B. McDonell, et al., *The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test.* Arch Intern Med., 1998. **158**(16): p. 1789-95.
44. Sallinen, J., S. Stenholm, T. Rantanen, et al., *Hand-grip strength cut points to screen older persons at risk for mobility limitation.* J Am Geriatr Soc, 2010. **58**(9): p. 1721-6.
45. Furler, L., [Validity and reliability of the pain questionnaire "Brief Pain Inventory". A literature research]. Pflege Z., 2013. **66**(9): p. 546-50.
46. Sharma, A., D.R. Hoover, Q. Shi, et al., *Frequent Occurrence of Pain and Prescription Opioid Use for Treatment of Pain Among Women with and at Risk for HIV Infection.* AIDS Behav, 2017. **19**(10): p. 017-1828.
47. Altman, D.G. and J.M. Bland, *Interaction revisited: the difference between two estimates.* BMJ., 2003. **326**(7382): p. 219.
48. Rothman, K., S. Greenland, and T.L. Lash, *Modern Epidemiology.* 1986, Philadelphia, PA: Lippincot Williams & Wilkins.
49. VanderWeele, T.J., *Explanation in Causal Inference: Methods for Mediation and Interaction.* 2015, New York, NY: Oxford University Press.
50. Reddy, P., K. Zuma, O. Shisana, et al., *Prevalence of tobacco use among adults in South Africa: Results from the first South African National Health and Nutrition Examination Survey.* S Afr Med J, 2015. **105**(8): p. 648-55.
51. Peltzer, K., A. Davids, and P. Njuho, *Alcohol use and problem drinking in South Africa: findings from a national population-based survey.* Afr J Psychiatry, 2010. **14**: p. 30-37.
52. Koyanagi, A., B. Stubbs, and D. Vancampfort, *Correlates of sedentary behavior in the general population: A cross-sectional study using nationally representative data from six low- and middle-income countries.* PLoS One., 2018. **13**(8): p. e0202222. doi: 10.1371/journal.pone.0202222. eCollection 2018.
53. Grover, K.W., A. Gonzalez, and M.J. Zvolensky, *HIV symptom distress and smoking outcome expectancies among HIV+ smokers: a pilot test.* AIDS Patient Care STDS., 2013. **27**(1): p. 17-21. doi: 10.1089/apc.2012.0333.
54. Tsui, J.I., D.M. Cheng, S.M. Coleman, et al., *Pain and Risk Behaviors Among HIV-Infected Persons in St. Petersburg, Russia.* AIDS Behav., 2017. **21**(6): p. 1775-1781. doi: 10.1007/s10461-016-1593-5.

55. Weinberger, A.H., E.K. Seng, J.W. Ditte, et al., *Perceived interrelations of pain and cigarette smoking in a sample of adult smokers living with HIV/AIDS*. *Nicotine Tob Res*, 2018. **31**(4830708).
56. Cioe, P.A., K.M. Guthrie, M.S. Freiberg, et al., *Cardiovascular Risk Reduction in Persons Living With HIV: Treatment Development, Feasibility, and Preliminary Results*. *J Assoc Nurses AIDS Care.*, 2018. **29**(2): p. 163-177. doi: 10.1016/j.jana.2017.11.007. Epub 2017 Dec 5.
57. Msisha, W.M., S.H. Kapiga, F. Earls, et al., *Socioeconomic status and HIV seroprevalence in Tanzania: a counterintuitive relationship*. *Int J Epidemiol.*, 2008. **37**(6): p. 1297-303. doi: 10.1093/ije/dyn186. Epub 2008 Sep 27.
58. Rzeszutek, M. and E. Gruszczynska, *Consistency of health-related quality of life among people living with HIV: Latent statetrait analysis*. *Health Qual Life Outcomes.*, 2018. **16**(1): p. 101. doi: 10.1186/s12955-018-0929-4.

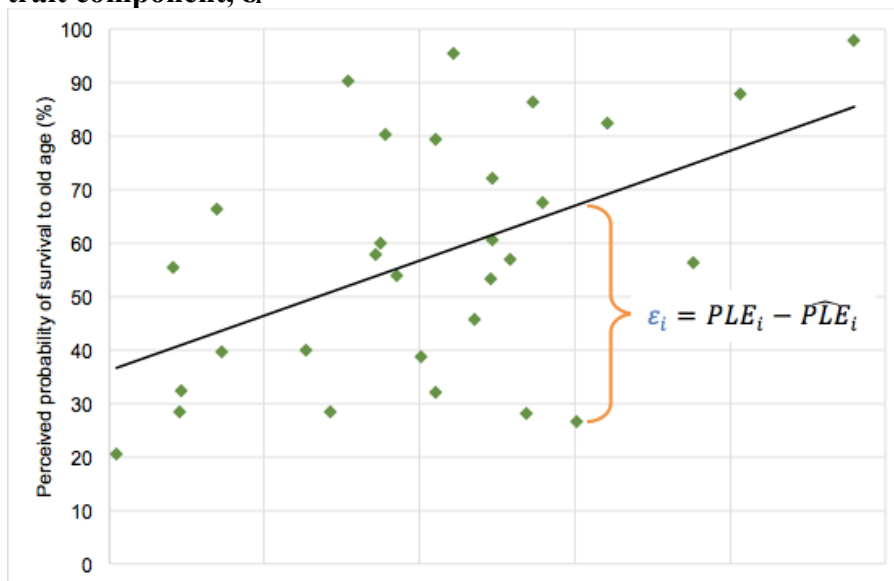
#### 4.8. Figures and Tables

**Figure 4.1 Conceptual diagram of relationship between HIV continuum stage, low perceived life expectancy (PLE) and CVD risk behaviors**



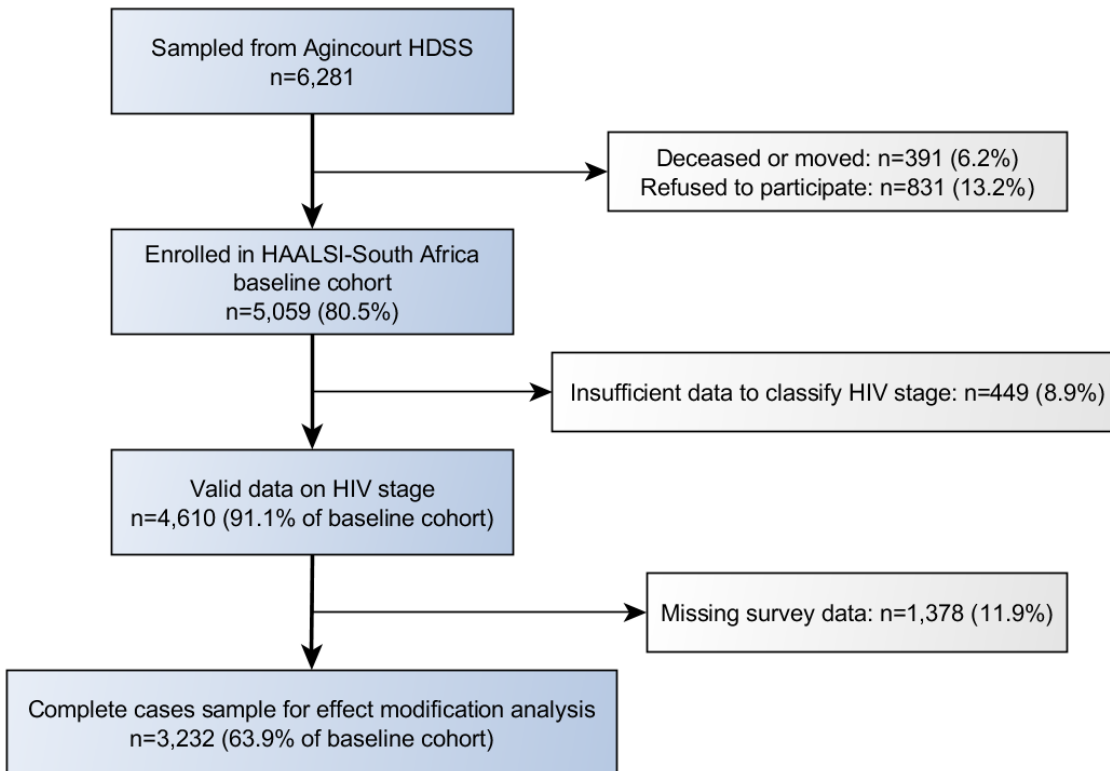
*Note: Bolded line indicates stronger pathways among individuals who are HIV+ and aware of their status but untreated, while dashed line indicates attenuated pathway among individuals who are HIV+ on treatment. Red arrows indicate confounding pathways and blue arrows indicate effect modification pathways.*

**Figure 4.2 Illustration of model for perceived life expectancy (PLE) and extraction of PLE trait component,  $\varepsilon_i$**



*Negative residuals represent individuals who believed they would die sooner than predicted based on others with the same profile of demographic and health-related characteristics used to estimate the regression line.*

**Figure 4.3 Sample eligibility flowchart for effect modification analysis**



Note: Insufficient data to classify HIV continuum stage was primarily due to refusing consent to dried blood spot (DBS) testing (7%) or invalid DBS test data (3%). Missing survey data was highest for perceived life expectancy (23%).

**Table 4.1 Sample characteristics**

Variable	Complete cases n=3,232 n (%)
<b>Demographics</b>	
Male	1,523 (47%)
Age group	1,523 (47%)
40-49	661 (20%)
50-59	972 (30%)
60-69	873 (27%)
70+	726 (22%)
Completed primary education	732 (23%)
Employed (full or part-time)	585 (18%)
Married	1,750 (54%)
Poorest 40% <sup>1</sup>	1,265 (39%)
<b>HIV-related</b>	
HIV continuum stage	
HIV–	2,395 (74%)
HIV+ unaware	225 (7%)
HIV+ aware untreated	79 (2%)
HIV+ on treatment	533 (16%)
Virally suppressed (among HIV+)	436 (54%)
<b>CVD risk behaviors</b>	
Tobacco smoking <sup>2</sup>	309 (10%)
Hazardous alcohol use <sup>3</sup>	317 (10%)
Sedentary behavior <sup>4</sup>	1,340 (41%)
<b>CVD history</b>	
Hypertension	1,323 (41%)
Dyslipidemia or heart disease	415 (13%)
Diabetes	219 (7%)
<b>Physiological symptoms<sup>5</sup></b>	
Muscle weakness	2,085 (65%)
Pain	258 (8%)
Cognitive difficulties (memory/concentration/learning)	1,353 (42%)
Physical dysfunction (difficulties with ADLs)	240 (7%)
<b>Psychological symptoms</b>	
Depressive symptoms (CESD-8 score 5+ out of 8)	221 (7%)
Low subjective well-being	869 (27%)
<b>Low perceived life expectancy (&lt;50%)</b>	<b>473 (15%)</b>

<sup>1</sup> Based on household wealth index.

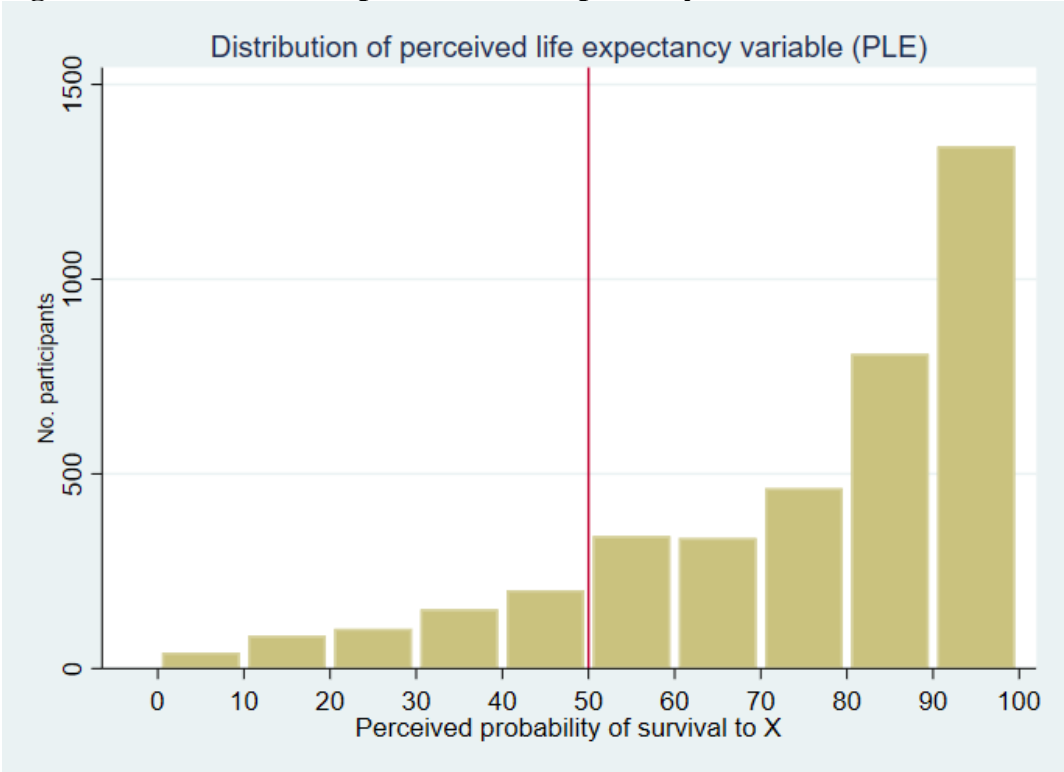
<sup>2</sup> Self-reported current use of smoking tobacco (cigarettes, cigars or pipes).

<sup>3</sup> AUDIT-C score >4 for men, >3 for women out of 7 total points.

<sup>4</sup> Does not meet criteria for minimal physical activity using IPAQ scoring.

<sup>5</sup> Physiological symptoms were included as determinants of perceived life expectancy for trait component extraction.

**Figure 4.4 Distribution of perceived life expectancy**



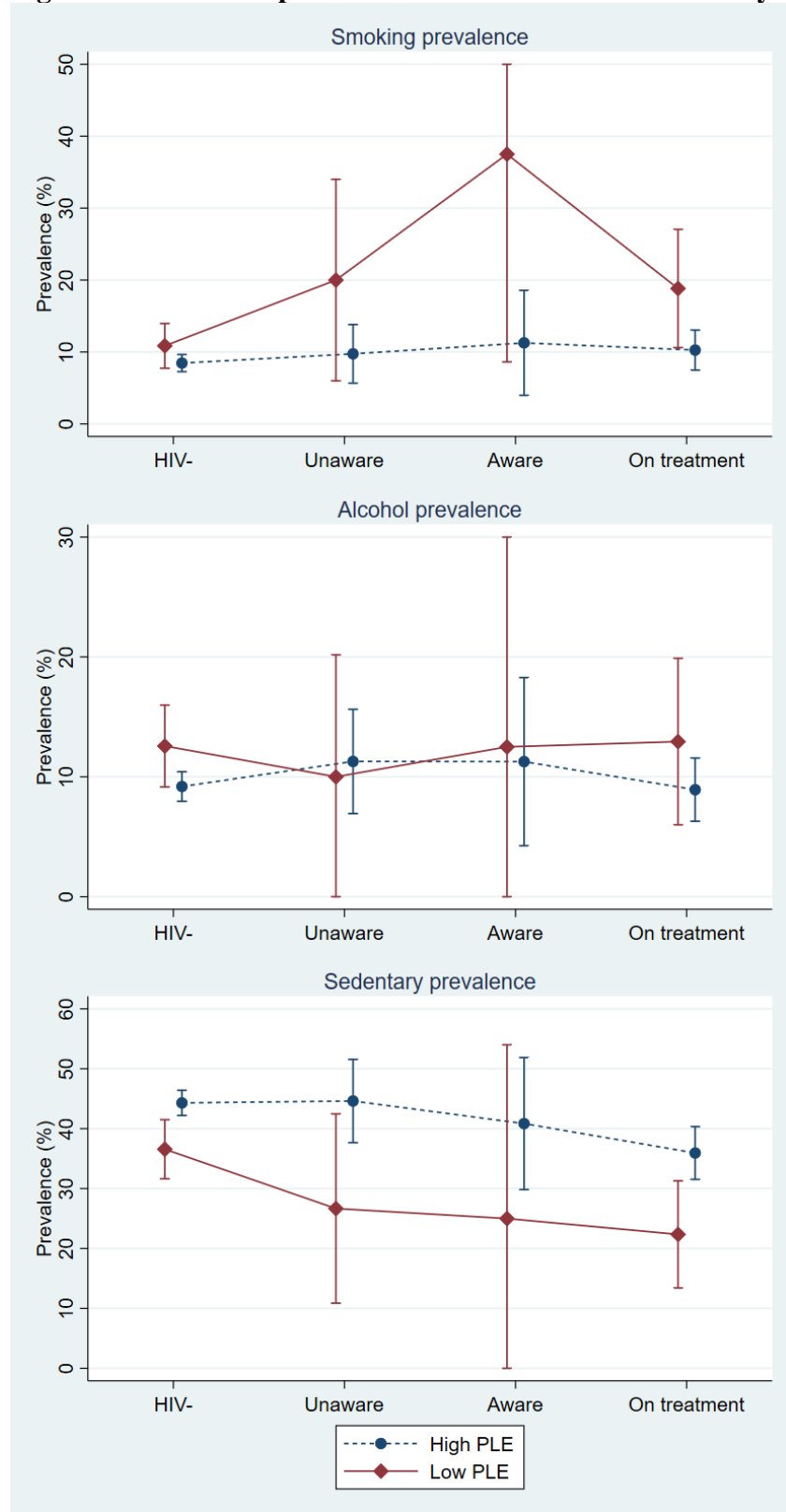
Note: X was an age between 80-100, chosen by the interviewer to be at least 10 years greater than the participant’s current age (median 25 years).

**Table 4.2 Prevalence ratios (PRs) for 3 CVD risk behaviors across joint categories of HIV continuum stage and perceived life expectancy (PLE) (n=3,232)**

Model Parameter	CVD risk behavior					
	Tobacco smoking		Hazardous alcohol use		Sedentary behavior	
	Unadjusted PR (95% CI)	Adjusted PR <sup>1</sup> (95% CI)	Unadjusted PR (95% CI)	Adjusted PR <sup>1</sup> (95% CI)	Unadjusted PR (95% CI)	Adjusted PR <sup>1</sup> (95% CI)
<b>HIV status</b>						
High PLE / HIV-	reference	reference	reference	reference	reference	reference
High PLE / HIV+	1.26 (0.97, 1.63)	0.98 (0.75, 1.27)	1.12 (0.86, 1.46)	1.02 (0.78, 1.33)	<b>0.87 (0.79, 0.97)</b>	0.97 (0.87, 1.08)
Low PLE / HIV-	<b>1.38 (1.01, 1.90)</b>	<b>1.54 (1.13, 2.09)</b>	1.34 (0.98, 1.82)	1.29 (0.95, 1.75)	<b>0.81 (0.70, 0.93)</b>	<b>0.76 (0.65, 0.87)</b>
Low PLE / HIV+	<b>2.18 (1.43, 3.33)</b>	<b>1.66 (1.10, 2.53)</b>	1.41 (0.85, 2.34)	1.32 (0.80, 2.16)	<b>0.58 (0.42, 0.80)</b>	<b>0.65 (0.47, 0.91)</b>
<b>HIV continuum stage</b>						
High PLE / HIV-	reference	reference	reference	reference	reference	reference
High PLE / HIV+ unaware	1.15 (0.73, 1.81)	0.86 (0.55, 1.34)	1.23 (0.81, 1.86)	1.07 (0.71, 1.61)	1.01 (0.85, 1.19)	1.13 (0.96, 1.33)
High PLE / HIV+ aware untreated	1.33 (0.68, 2.60)	1.05 (0.54, 2.05)	1.23 (0.63, 2.39)	1.20 (0.63, 2.28)	0.92 (0.69, 1.22)	1.03 (0.79, 1.36)
High PLE / HIV+ on treatment	1.21 (0.89, 1.65)	0.97 (0.71, 1.32)	0.97 (0.70, 1.35)	0.90 (0.65, 1.25)	<b>0.81 (0.71, 0.93)</b>	0.90 (0.79, 1.03)
Low PLE / HIV-	1.28 (0.92, 1.79)	<b>1.43 (1.03, 1.97)</b>	<b>1.37 (1.00, 1.86)</b>	1.33 (0.98, 1.81)	<b>0.83 (0.71, 0.96)</b>	<b>0.77 (0.67, 0.89)</b>
Low PLE / HIV+ unaware	<b>2.36 (1.14, 4.91)</b>	1.72 (0.84, 3.53)	1.09 (0.37, 3.21)	1.04 (0.37, 2.91)	0.60 (0.33, 1.09)	0.69 (0.38, 1.25)
Low PLE / HIV+ aware untreated	<b>4.43 (1.79, 10.97)</b>	<b>3.09 (1.40, 6.83)</b>	1.36 (0.22, 8.55)	1.36 (0.23, 8.14)	0.56 (0.17, 1.88)	0.66 (0.21, 2.12)
Low PLE / HIV+ on treatment	<b>2.22 (1.40, 3.54)</b>	<b>1.81 (1.13, 2.86)</b>	1.41 (0.80, 2.48)	1.26 (0.73, 2.20)	<b>0.50 (0.34, 0.75)</b>	<b>0.55 (0.37, 0.83)</b>

<sup>1</sup> Prevalence ratios were adjusted for age, education (at least primary), employed (full or part-time), wealth index (poorest 40% vs. richest 60%), hypertension, dyslipidemia, and diabetes. Bolded estimates are significant at  $\alpha < 0.05$ .

**Figure 4.5 Predicted prevalence of 3 CVD risk behaviors by HIV continuum stage and PLE**



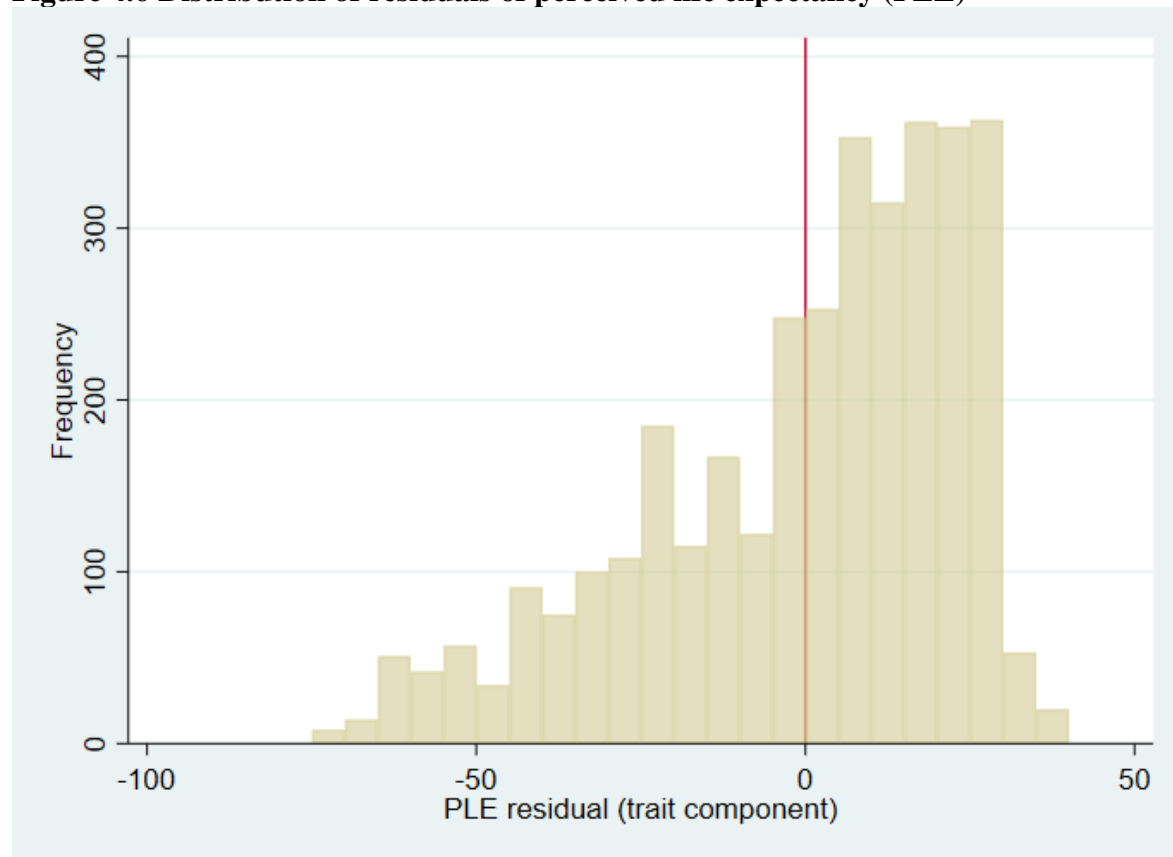
Model-predicted prevalences are adjusted for age, education (at least primary), employed (full or part-time), wealth index (poorest 40% vs. richest 60%), hypertension, dyslipidemia, and diabetes.

**Table 4.3 Regression model to extracting PLE trait component (residuals)**

<b>Perceived life expectancy (%)</b>	<b>Coefficient (95% CI)</b>
<b>Demographics</b>	
Male	-0.80 (-2.56, 0.97)
Age	0.03 (-0.05, 0.11)
Completed primary education	3.31 (1.11, 5.50)
Employed (full or part-time)	-0.01 (-2.29, 2.26)
Poorest 40%	-0.61 (-2.33, 1.12)
<b>Traditional CVD risk factors</b>	
Hypertension	0.53 (-1.22, 2.27)
Dyslipidemia	0.85 (-1.59, 3.30)
Diabetes	-1.98 (-5.29, 1.33)
<b>Physiological HIV symptoms</b>	
Weakness	-1.54 (-3.48, 0.39)
Pain	0.01 (-3.01, 3.02)
Physical dysfunction	-6.40 (-9.54, -3.25)
Cognitive impairment	-1.39 (-3.08, 0.31)
<b>Intercept</b>	<b>76.69 (71.59, 81.79)</b>

% variance explained ( $r^2$ ): 7.5%

**Figure 4.6 Distribution of residuals of perceived life expectancy (PLE)**



Note: vertical line denotes cut-point for classifying individual as pessimistic (<0) vs. optimistic ( $\geq 0$ ) trait

**Table 4.4. Concordance between low perceived life expectancy (PLE) as measured and trait component**

	Optimistic trait (residual $\geq 0$ )	Pessimistic trait (residual $< 0$ )
	n (row %)	n (row %)
High PLE ( $> 50\%$ )	2,063 (70%)	884 (30%)
Low PLE ( $\leq 50\%$ )	0 (0%)	509 (100%)

**Table 4.5 Sensitivity analyses for alternative PLE definitions: tobacco smoking**

	<b>Tobacco smoking</b>		
	PLE as measured (n=3,232)	Re-classify missing PLE as low PLE (n=4,610)	PLE trait component (n=3,232)
	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)
<b>HIV status</b>			
High PLE / HIV-	reference	reference	reference
High PLE / HIV+	0.98 (0.75, 1.27)	0.97 (0.75, 1.27)	0.96 (0.69, 1.33)
Low PLE / HIV-	<b>1.54 (1.13, 2.09)</b>	<b>1.28 (1.01, 1.62)</b>	1.27 (0.99, 1.63)
Low PLE / HIV+	<b>1.66 (1.10, 2.53)</b>	1.05 (0.74, 1.49)	1.31 (0.95, 1.81)
<b>HIV continuum stage</b>			
High PLE / HIV-	reference	reference	reference
High PLE / HIV+ unaware	0.86 (0.55, 1.34)	0.86 (0.55, 1.33)	0.93 (0.56, 1.56)
High PLE / HIV+ aware untreated	1.05 (0.54, 2.05)	1.03 (0.53, 2.02)	0.56 (0.18, 1.74)
High PLE / HIV+ on treatment	0.97 (0.71, 1.32)	0.97 (0.71, 1.32)	1.02 (0.70, 1.50)
Low PLE / HIV-	<b>1.43 (1.03, 1.97)</b>	1.23 (0.97, 1.57)	1.25 (0.97, 1.61)
Low PLE / HIV+ unaware	1.72 (0.84, 3.53)	1.02 (0.55, 1.88)	1.17 (0.66, 2.08)
Low PLE / HIV+ aware untreated	<b>3.09 (1.40, 6.83)</b>	1.77 (0.81, 3.87)	<b>2.65 (1.49, 4.72)</b>
Low PLE / HIV+ on treatment	<b>1.81 (1.13, 2.86)</b>	1.09 (0.73, 1.63)	1.23 (0.85, 1.79)

<sup>1</sup> Prevalence ratios were adjusted for age, education (at least primary), employed (full or part-time), wealth index (poorest 40% vs. richest 60%), hypertension, dyslipidemia, and diabetes. Bolded estimates are significant at  $\alpha < 0.05$ .

**Table 4.6 Sensitivity analyses for alternative PLE definitions: hazardous alcohol use**

	<b>Hazardous alcohol use</b>		
	PLE as measured (n=3,232)	Re-classify missing PLE as low PLE (n=4,610)	PLE trait component (n=3,232)
	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)
<b>HIV status</b>			
High PLE / HIV-	reference	reference	reference
High PLE / HIV+	1.02 (0.78, 1.33)	1.02 (0.78, 1.32)	1.03 (0.75, 1.42)
Low PLE / HIV-	1.29 (0.95, 1.75)	1.07 (0.85, 1.36)	1.11 (0.87, 1.42)
Low PLE / HIV+	1.32 (0.80, 2.16)	0.92 (0.63, 1.34)	1.05 (0.74, 1.50)
<b>HIV continuum stage</b>			
High PLE / HIV-	reference	reference	reference
High PLE / HIV+ unaware	1.07 (0.71, 1.61)	1.07 (0.71, 1.61)	1.09 (0.67, 1.76)
High PLE / HIV+ aware untreated	1.20 (0.63, 2.28)	1.19 (0.63, 2.27)	1.22 (0.58, 2.56)
High PLE / HIV+ on treatment	0.90 (0.65, 1.25)	0.90 (0.65, 1.25)	0.91 (0.60, 1.36)
Low PLE / HIV-	1.33 (0.98, 1.81)	1.09 (0.86, 1.37)	1.12 (0.88, 1.44)
Low PLE / HIV+ unaware	1.04 (0.37, 2.91)	1.07 (0.58, 1.96)	1.04 (0.56, 1.94)
Low PLE / HIV+ aware untreated	1.36 (0.23, 8.14)	0.94 (0.24, 3.63)	1.18 (0.42, 3.33)
Low PLE / HIV+ on treatment	1.26 (0.73, 2.20)	0.77 (0.48, 1.24)	0.97 (0.64, 1.47)

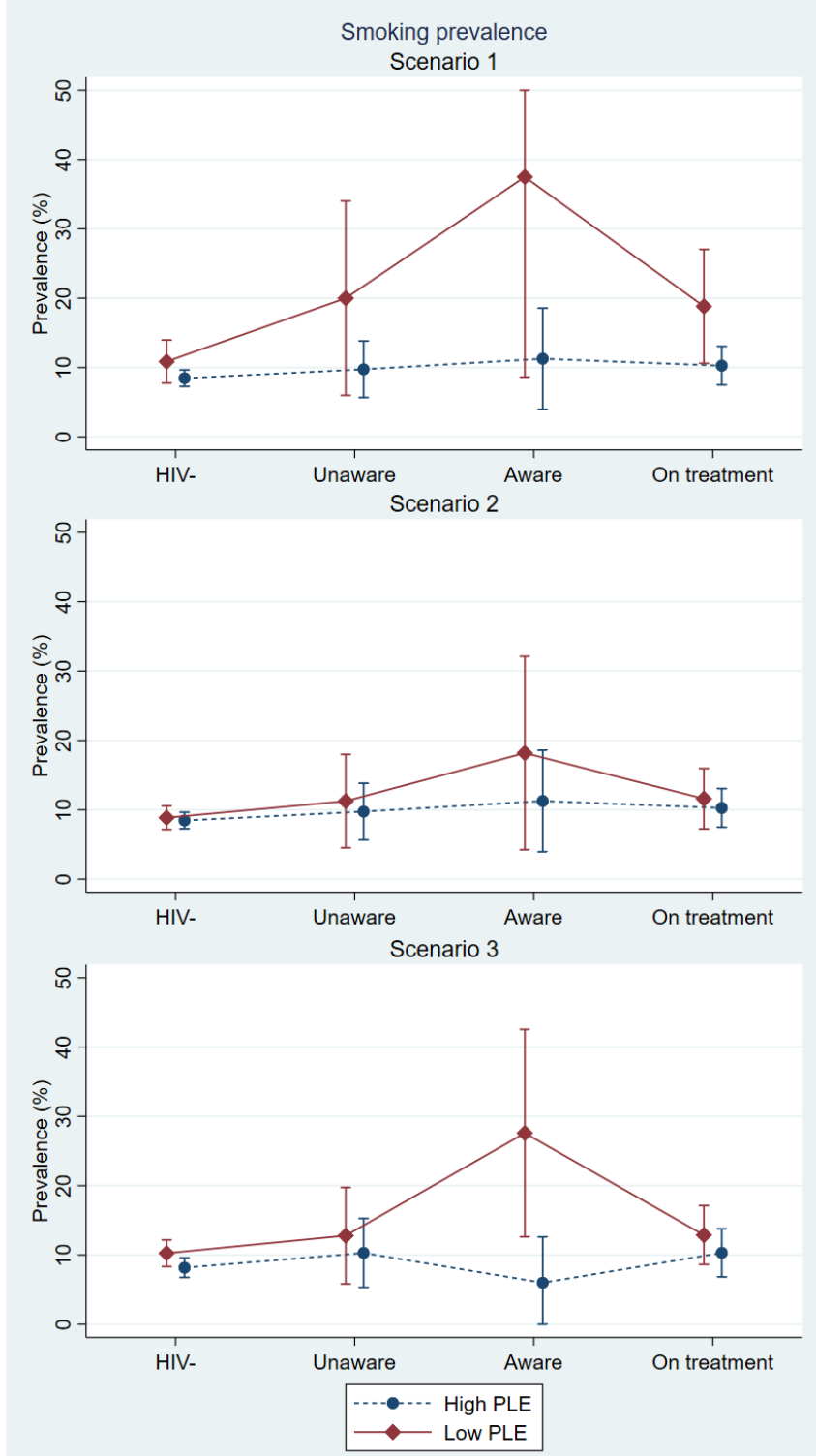
<sup>1</sup> Prevalence ratios were adjusted for age, education (at least primary), employed (full or part-time), wealth index (poorest 40% vs. richest 60%), hypertension, dyslipidemia, and diabetes. Bolded estimates are significant at  $\alpha < 0.05$ .

**Table 4.7 Sensitivity analyses for alternative PLE definitions: sedentary behavior**

	Sedentary behavior		
	PLE as measured (n=3,232)	Re-classify missing PLE as low PLE (n=4,610)	PLE trait component (n=3,232)
	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)	Adjusted PR <sup>1</sup> (95% CI)
<b>HIV status</b>			
High PLE / HIV-	reference	reference	reference
High PLE / HIV+	<b>0.87 (0.79, 0.97)</b>	0.99 (0.89, 1.10)	0.96 (0.84, 1.09)
Low PLE / HIV-	<b>0.81 (0.70, 0.93)</b>	<b>0.91 (0.84, 0.99)</b>	<b>0.82 (0.75, 0.91)</b>
Low PLE / HIV+	<b>0.58 (0.42, 0.80)</b>	<b>0.84 (0.71, 0.99)</b>	<b>0.79 (0.66, 0.93)</b>
<b>HIV continuum stage</b>			
High PLE / HIV-	reference	reference	reference
High PLE / HIV+ unaware	1.13 (0.96, 1.33)	1.15 (0.97, 1.36)	1.13 (0.94, 1.37)
High PLE / HIV+ aware untreated	1.03 (0.79, 1.36)	1.06 (0.80, 1.39)	1.01 (0.73, 1.39)
High PLE / HIV+ on treatment	0.90 (0.79, 1.03)	0.92 (0.80, 1.05)	<b>0.85 (0.72, 0.99)</b>
Low PLE / HIV-	<b>0.77 (0.67, 0.89)</b>	<b>0.92 (0.84, 0.99)</b>	<b>0.82 (0.74, 0.91)</b>
Low PLE / HIV+ unaware	0.69 (0.38, 1.25)	0.90 (0.68, 1.19)	0.85 (0.63, 1.15)
Low PLE / HIV+ aware untreated	0.66 (0.21, 2.12)	0.44 (0.18, 1.06)	0.85 (0.52, 1.39)
Low PLE / HIV+ on treatment	<b>0.55 (0.37, 0.83)</b>	<b>0.81 (0.66, 0.99)</b>	<b>0.75 (0.61, 0.92)</b>

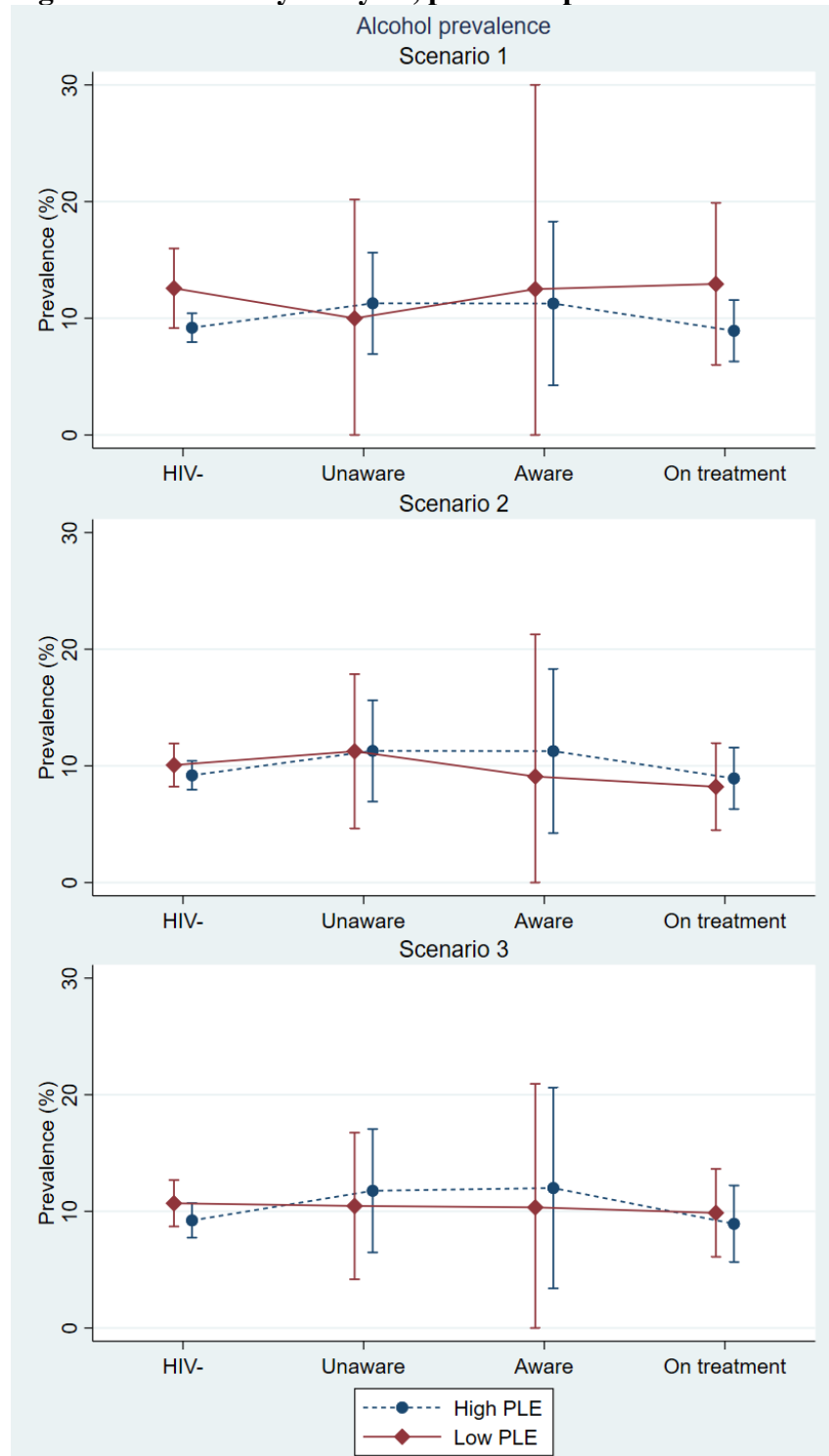
<sup>1</sup> Prevalence ratios were adjusted for age, education (at least primary), employed (full or part-time), wealth index (poorest 40% vs. richest 60%), hypertension, dyslipidemia, and diabetes. Bolded estimates are significant at  $\alpha < 0.05$ .

**Figure 4.7 Sensitivity analyses, predicted prevalence of smoking**



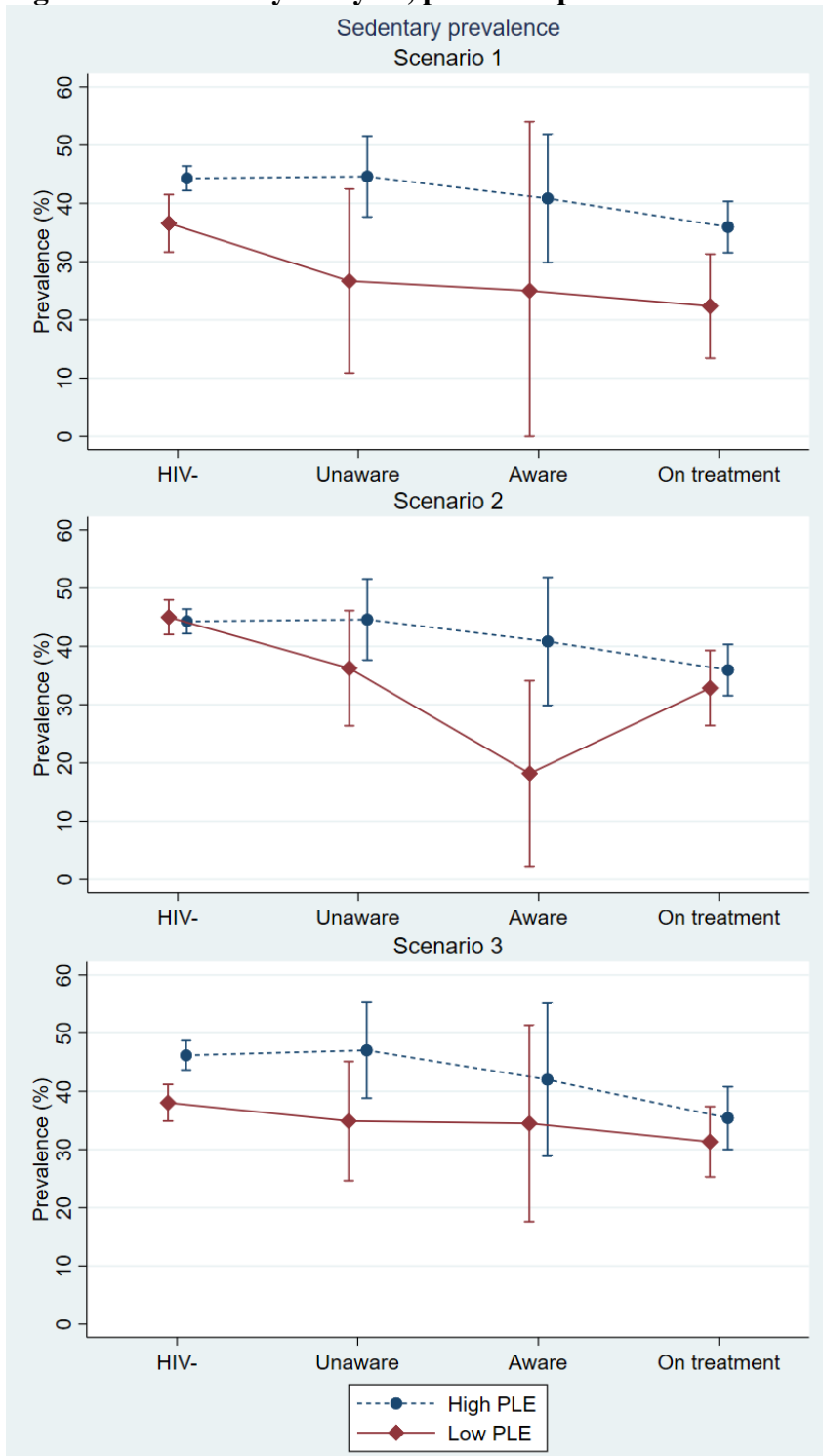
Note: scenario 1: PLE as measured, scenario 2: observations with missing PLE assumed to have low PLE, scenario 3: PLE trait component

**Figure 4.8 Sensitivity analyses, predicted prevalence of hazardous alcohol use**



Note: scenario 1: PLE as measured, scenario 2: observations with missing PLE assumed to have low PLE, scenario 3: PLE trait component

**Figure 4.9 Sensitivity analyses, predicted prevalence of sedentary behavior**



Note: scenario 1: PLE as measured, scenario 2: observations with missing PLE assumed to have low PLE, scenario 3: PLE trait component

## **CHAPTER 5. CONCLUSION**

### **5.1. Overview**

The overarching goal of this dissertation was to explore the causal relationship of HIV on CVD risk behaviors. This research question was motivated by qualitative evidence that people living with HIV (PLWH) often report adopting unhealthy behaviors as a means of coping with HIV-related stress, and supported by established stress-coping theories in the psychological literature. To date, limited research attention had been devoted to CVD risk behaviors as an outcome of HIV overall, a gap which is especially notable for dietary and sedentary behaviors, and few of the available studies had quantitatively tested the stress-coping hypotheses previously mentioned. Furthermore, as per self-regulation theory, we hypothesized that perceived life expectancy (PLE) had a potential modifying role on the relationship between HIV and CVD risk behaviors. In addition, this study aimed to improve upon prior research in this area by contrasting the effects of HIV infection itself vs. the effects of awareness of one's status and of being on treatment (i.e., using an HIV continuum approach). Evidence suggests different types of stress are experienced at each HIV continuum stage, yet existing studies use varied and often inadequate measures of HIV, resulting in imprecision in how study results are described and difficulties in synthesizing results across studies. This dissertation addressed these gaps via a systematic review of the literature and empirically using data from a population-based cohort of older adults in South Africa.

### **5.2. Summary**

In chapter 2, we systematically reviewed the available quantitative literature in support of an effect of HIV on CVD risk behaviors. Our review found that comparatively little research

attention had been placed on CVD risk behaviors as an outcome of, as opposed to a risk factor for HIV. Unsurprisingly, therefore, few longitudinal studies had been conducted on this topic, making concerns regarding temporality commonplace. Exposure measurement was also found to be highly variable and inconsistent across studies. In particular, the available measures were rarely equipped to differentiate effects across HIV continuum stages or were inadequately described. Few studies were conducted on dietary and sedentary behaviors among HIV-positive populations overall. Nonetheless, the available literature suggested that being HIV-positive was associated with higher risk of smoking and alcohol use. While some studies observed improvements in CVD risk behaviors immediately following receipt of a new diagnosis or initiation of HIV care, evidence suggested that these improvements were unlikely to be sustained long-term.

In chapter 3, we used data from a population-based sample of adults aged 40 years and older in rural Agincourt district, South Africa, to explore patterns across the HIV continuum of three CVD risk behaviors, smoking, hazardous alcohol use and sedentary behaviors. As a secondary objective, we tested whether several proposed measures of physiological and/or psychological stress mediated the observed associations. We hypothesized a priori that CVD risk behaviors would be more prevalent among HIV-positive than HIV-negative individuals due to the physical toll of HIV symptoms; more prevalent among individuals who are aware vs. unaware of their status; and less prevalent among those on treatment due to the known salutary effects of antiretroviral drugs. We found that the prevalence of smoking, but not hazardous alcohol use nor sedentary behavior, were consistent with these patterns. However, due to low power, even the patterns of smoking were not statistically significant for all HIV continuum stage comparisons. Results differed by sex, in part due to low self-reported rates of smoking and hazardous alcohol

use among women. Lastly, our findings were not consistent with mediation hypotheses for any of the proposed mediators and thus did not support the stress-coping hypothesis.

In chapter 4, we used data from the above-mentioned study to assess whether self-reported PLE modified the observed relationships. We hypothesized that individuals with low levels of PLE would assume that they would derive fewer benefits from CVD prevention and therefore be more likely to adopt unhealthy behaviors as a result of being HIV-positive. To test this hypothesis, we examined CVD risk behavior patterns across joint levels of HIV continuum stage and low vs. high PLE. Results from this analysis showed that low PLE was a strong independent predictor of smoking and that the patterns of smoking were stronger among individuals with low vs. high PLE. As in chapter 3, low power resulted in difficulties detecting significant findings that were consistent with our hypothesis, with the exception being for smoking.

### **5.3. Strengths and limitations**

This dissertation has several strengths. The systematic review from chapter 2 reiterated an important and often unstated knowledge gap regarding the evidence of differences in CVD risk behaviors by HIV status. Causal claims regarding the relationship between HIV and CVD risk behaviors remain commonplace, despite the inadequacy of the supporting data. To our knowledge, the analyses presented in Chapters 3 and 4 are the first to quantitatively test stress-coping mechanisms that had been proposed based on prior qualitative research on CVD risk behaviors among PLWH. As a result, this dissertation tested novel mediation and effect modification analyses, supported firmly by established theory, and included a more comprehensive set of explanatory variables (i.e., physiological and psychological measures) than those considered in previous studies. Similarly, the analysis in Chapter 4 was the first to examine

the role of PLE on HIV-related outcomes. This dissertation was also the first to our knowledge to utilize the full HIV continuum to adequately distinguish between infection, awareness and treatment statuses. Though our findings did not support significant and consistent differences across stages, this approach could be used in future research to improve inference in HIV research. Lastly, the analyses in Chapters 3 and 4 were enhanced by strengths of the sample population: (1) population-representativeness, which mitigated important and widespread selection biases and generalizability issues in the clinic-based samples predominantly used in other studies; (2) restricted to older adults, a population of particular interest for aging-related health conditions; and (3) located in rural sub-Saharan Africa, an understudied region with respect to HIV comorbidities such as CVD.

This dissertation also had several limitations. First, although the analytic methods aimed to address temporality issues via the HIV continuum approach, the cross-sectional nature of the data precludes establishment of temporality. Second, the main outcome measures were self-reported which was likely to be subject to reporting bias that could have been differential by HIV continuum stage. Third, while we attempted to ground our hypotheses within established theory, the motivation for one's healthy or unhealthy behaviors was not explicitly measured. Thus, the internal decision-making process underlying an individual's observed behavior remains an area of speculation (indeed, it would remain so even if the behaviors themselves were not self-reported). Fourth, we used a novel measure of PLE in Chapter 4, which raises questions regarding its construct validity. A key source of uncertainty is the extent to which PLE is itself influenced by HIV and other changes in health or life circumstances, the state-trait distinction explored in Chapter 4. We attempted to extract the trait component of PLE as a sensitivity

analysis; however, the analytic approach was adapted from other methods that use repeated measures. Thus, it relied on stronger assumptions and was itself novel and unvalidated.

#### **5.4. Implications for public health and future research**

As CVD prevention increasingly becomes a public health priority for HIV-positive populations, unhealthy lifestyle behaviors, which are prevalent and modifiable, represent potentially high-yield targets for intervention. However, the limited success achieved to date suggests a need to better understand the underlying motivations for lifestyle behaviors. Understanding the influence of HIV itself on CVD risk behavior engagement and its mechanisms is crucial for identifying etiology and developing interventions.

Findings from this dissertation did not follow the patterns of CVD risk behavior engagement by HIV continuum stage we hypothesized a priori, with the exception of elevated smoking among the HIV-positive aware untreated group. Findings also did not provide evidence in support of physiological or psychological stress-coping mechanisms as hypothesized. While it is possible that smoking is simply more likely to be adopted by HIV-positive individuals in the presence of stress, inconsistent findings across CVD risk behaviors prompts further research that may better test such hypotheses or uncover alternative explanations for null findings. However, it did reveal a potentially important role of PLE, where high levels of PLE may act as a buffer against the negative effects of HIV, particularly for smoking. This finding suggests that additional support to bolster optimism about one's future, in complement with ART treatment initiation strategies, might enhance behavior modification for CVD prevention; future work will be required to empirically test such interventions. Finally, given the lifelong nature of HIV infection, further

studies should follow this example and use the continuum perspective that takes into account the entire HIV continuum to improve inference.

## APPENDICES

### Appendix Table 5.1 Search terms used in systematic literature review

#### Pubmed/MEDLINE

(smoking[Title/Abstract] OR tobacco[Title/Abstract] OR alcohol[Title/Abstract] OR diet[Title/Abstract] OR fruit[Title/Abstract] OR vegetable[Title/Abstract] OR nutrition[Title/Abstract] OR exercise[Title/Abstract] OR "physical activity"[Title/Abstract]) AND (incidence OR prevalence OR prevalent) AND (change OR difference OR modif\* OR reduc\* OR association) AND ("people living with HIV" OR "HIV-infected" OR "HIV-positive" OR "antiretroviral therapy" or "HIV diagnosis" or "HIV status") AND English[Language] AND ("2000"[Date - Publication] : "3000"[Date - Publication])

#### Web of Science

TS=((smoking OR tobacco OR alcohol OR diet OR fruit OR vegetable OR nutrition OR exercise OR "physical activity") AND (incidence OR prevalence OR prevalent) AND (change OR difference OR modif\* OR reduc\*)) AND ("people living with HIV" OR "HIV-infected" OR "HIV-positive" OR "antiretroviral therapy" or "HIV diagnosis" or "HIV status")) AND PY=(2000-2018)

Refined by: DOCUMENT TYPES: ( ARTICLE ) AND LANGUAGES: ( ENGLISH )

Timespan: 2000-2018.

#### PsycINFO

((smoking or tobacco or alcohol or diet or fruit or vegetable or nutrition or exercise or "physical activity") and (incidence or prevalence or prevalent) and (change or difference or modif\* or reduc\* or association) and ("people living with HIV" or "HIV-infected" or "HIV-positive" or "antiretroviral therapy" or "HIV diagnosis" or "HIV status")).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures] limit to (english language and yr="2000 - 2017")

#### EMBASE/MEDLINE

(smoking OR tobacco OR alcohol OR diet OR fruit OR vegetable OR nutrition OR exercise OR 'physical activity') AND (incidence OR prevalence OR prevalent) AND (change OR difference OR modif\*) AND ('people living with hiv' OR 'hiv-infected' OR 'hiv-positive' OR "HIV diagnosis" OR "HIV status") AND [article]/lim AND [english]/lim AND [embase]/lim AND [2000-2017]/py

**Appendix Table 5.2 Cross-sectional analyses of smoking by HIV continuum stage**

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Smoking measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
1	Aralis et al. (2018)	Los Angeles, United States	18-45yo HIV+ African American and Hispanic MSM (n=155)	Community-based	Cross-sectional	Smoking, current (self-report)	VLS (blood test)	VLS among smokers vs. non-smokers	VLS by smoking: adjusted OR = 0.48 (0.24, 0.93)	age, race/ethnicity
2	Bekele et al. (2017)	Ontario, Canada	HIV+ patients in care (n=4,473)	Clinic-based (Ontario HIV Treatment Network Cohort Study)	Cross-sectional*	Smoking (self-report: current)	CD4 count category (<200 vs. 200-499 vs. 500+)	Smoking among CD4 <200 vs. 200-499 vs. ≥500	prevalence = 41% vs. 39% vs. 39% (chi-sq trend p=0.615)	age, sex, race/ethnicity, relationship status, country of birth, education, employment, alcohol use, drug use, depression/anxiety
							VLS (medical records: <50 copies/ml)	Smoking among VLS vs. not VLS	prevalence = 35% vs. 44% (Kruskal Wallis p<.001)	
							ART use (medical records)	Smoking among ART users vs. non-users	38% vs. 45% (chi-sq p<.001)	
							HIV+ vs. general population	Smoking among HIV+ vs. general population	prevalence = 39.2% vs. 13%; adjusted PR = 3.0 (p<.001)	
3	Benard et al. (2006)	Aquitaine, France	HIV+ persons (n=2,036)	Clinic-based	Cross-sectional	Regular smoking, past year (self-report: >1 cigarette/day WHO definition)	Length of HIV infection, 5-10 vs. 0-5 years (medical records)	Regular smoking among length of HIV infection 5-10 vs. 0-5 yrs	adjusted OR = 1.46 (1.10, 1.94)	sex, age, HIV transmission categories, CD4, ART duration, duration of HIV infection
							CD4≤350 & VL≥1000 vs. other (medical records)	Regular smoking among CD4≤350 & VL≥1000 vs. other†	adjusted OR = 0.81 (0.67, 0.98)	
							ART duration 3-6 vs. 0 yrs (medical records)	Regular smoking among ART duration 3-6years vs. 0	adjusted OR = 1.51 (1.04, 2.20)	
							HIV+ vs. HIV- (general population)	Regular smoking among HIV+ vs. HIV-	prevalence = 79% vs. 34% (p<.001)	
4	Bergersen et al. (2004)	Oslo, Norway	HIV+ persons on ART (n=219) and not on ART (n=64) and HIV-controls (n=438)	Clinic-based (Oslo HIV Cohort Study)	Cross-sectional	Daily smoking (self-report)	HIV/ART status (medical records: HIV+ ART+ vs. HIV+ ART- vs. HIV- controls)	Smoking by HIV/ART status (ART+ vs. ART- vs. HIV-)	prevalence = 54.5% vs. 56.3% vs. 30.1% (p<0.01)	not stated

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Smoking measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
5	Brath et al. (2016)	Austria and Germany	HIV+ patients in care (n=477)	Clinic-based	Cross-sectional	Smoking past 7 days (exhaled CO)	CDC stage of HIV infection (self-report: acute HIV vs. latent HIV vs. AIDS)	Smoking among HIV stage (acute vs. latent vs. AIDS)	prevalence = 56% vs. 24% vs. 17% (chi-sq p=0.627)	age, sex, IDU, CVD, education, ART use, relationship status, partner smoking status
						Readiness to quit smoking (self-report)	ART status (self-report)	Smoking among ART users vs. non-users	adjusted OR = 0.55 (0.27, 1.09)	
								Ready to quit among ART users vs. non-users	adjusted OR = 1.29 (0.50, 3.30)	
6	Brown et al. (2017)	St. Petersburg, Russia	HIV+ women prescribed ART (n=150)	Clinic-based	Cross-sectional	Frequent smoking, past month (self-report: $\geq 20$ vs. $<20$ days)	CD4 count (biomarker) VL undetectable (biomarker)	CD4 count among frequent vs. infrequent smokers	mean difference = -25.5 (p=0.57)	ART adherence, length of HIV diagnosis
						Heavy/moderate smoking, past month (self-report: $\geq 10$ /day)		CD4 count among heavy/moderate vs. light smokers	mean difference = -58.3 (p=0.12)	
								Undetectable VL among frequent vs. infrequent smokers <sup>†</sup>	adjusted OR = 0.63 (p<.001)	
								Undetectable VL among heavy/moderate vs. light smokers	adjusted OR = 0.43 (p<.001)	
7	Burkhalter et al. (2005)	New York, United States	Medicaid HIV+ patients in care (n=428)	Clinic-based	Cross-sectional (baseline assessments from longitudinal study)	Smoking (self-report: current vs. former vs. never)	Symptomatic (symptomatic HIV or CDC-defined AIDS vs. asymptomatic HIV)	Symptomatic HIV/AIDS among current vs. never smokers	prevalence = 69% vs. 60%	unadjusted
8	De Socio et al. (2007)	Perugia, Italy	HIV+ patients in care (n=403) and general population controls (n=96)	Clinic-based (HIV+) and population-based (general population)	Cross-sectional	Smoking (self-report, current)	HIV status (biomarker) & ART use (medical records)	Smoking among HIV- vs. HIV untreated vs. HIV treated	28% vs. 60% vs. 53% (chi-sq p-value<0.001)	unadjusted
9	Duval et al. (2008)	France	HIV+ patients in care (n=727)	Clinic-based	Cross-sectional	Smoking, past 6 months (self-report: active vs. none)	CD4 (self-report: $>500$ vs. $<200$ )	CD4 $>500$ among smokers vs. non-smokers	adjusted prevalence = 47% vs. 38% (p=0.0583)	age, sex, BMI, smoking, IDU, disclosure of HIV status, illicit drug use

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Smoking measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
10	Elf et al. (2017)	Klerksdorp, South Africa	HIV patients in care (n=1210)	Clinic-based	Cross-sectional	Smoking (composite of self-report, exhaled CO, and urine cotinine)	Undetectable VL (blood test)	Smoking among undetectable vs. detectable VL <sup>†</sup>	adjusted OR = 0.59 (0.40, 0.91)	age, employment, income, household characteristics, BMI, alcohol use
11	Etukumana et al. (2010)	Zawan, Nigeria	Pregnant women in antenatal care (n=350)	Clinic-based	Cross-sectional	Smoking (self-report: current)	HIV infection status (blood test)	Smoking among HIV+ vs. HIV-	adjusted OR = 0.0 (0.0, 12.6)	not stated
12	Gutierrez et al. (2013)	United States	20-49yo HIV+ (n=76) and HIV- adults (n=12263)	Population-based (NHANES)	Cross-sectional	Smoking (self-report: current)	HIV status (blood test or self-reported ART use)	Smoking among HIV+ vs. HIV-	adjusted OR = 2.1 (0.8, 5.5)	sex, ethnicity, educational attainment, family income
13	Jaquet et al. (2009)	Multi-country, Africa (Cote d'Ivoire, Benin, Mali)	HIV+ patients on ART (n=2920)	Clinic-based (IeDEA)	Cross-sectional	Regular smoking (self-report; past year)	Low CD4 count <50 (medical records, prior to ART initiation)	Regular smoking among high vs. low CD4 <sup>†</sup>	adjusted OR = 0.67 (0.50, 0.91)	country, sex, marital status, alcohol use, age, formal education, household income, TB infection
14	Luo et al. (2014)	Yunnan Province, China	16+yo HIV+ persons in rural Dai and Jingpo communities (n=455)	Community-based	Cross-sectional	Smoking, past 3 days (self-report)	ART use, current (self-report)	Current smoking among ART users vs. non-users	adjusted OR = 0.51 (0.17, 1.58)	age, sex, ethnicity, marital status, education, drinking, drug use
						Heavy smoking, past 3 days (self-report)		Heavy smoking among ART users vs. non-users	adjusted OR = 1.56 (0.88, 2.76)	
15	Mdege et al. (2017)	Multi-country	15-59yo HIV+ men (n=6729), 15-49yo HIV+ women (n=11495), and HIV- men and women (n=193763, n=222808)	Population-based (Demographic and Health Surveys)	Cross-sectional	Smoking (self-report)	HIV status (blood test)	Tobacco use among HIV+ vs. HIV-	adjusted RR (men) = 1.46 (1.30, 1.65); adjusted RR (women) = 1.90 (1.38, 2.62)	country-level covariates, survey year
16	Mdodo et al. (2015)	United States	HIV+ patients in care (n=4217), and adult general population	Clinic-based (HIV+) and population-based (National Health Interview)	Cross-sectional	Smoking, current (self-report)	HIV+ vs. HIV- (general population)	Smoking prevalence among HIV+ vs. HIV-	prevalence = 37.6% vs. 20.6%; difference = 17.0% (14.0, 20.1); p<0.001	age, sex, race/ethnicity, education, poverty

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Smoking measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
			(n=27731)	Survey)		Quit attempt, ever (self-report)		Quit rates among HIV+ vs. HIV-	Lower quit rate among HIV+: no statistical test performed	
17	Oka et al. (2013)	Tokyo, Japan	HIV+ patients in care (n=100)	Hospital-based (HIV+) and population-based (National Nutrition Survey)	Cross-sectional	Smoking (self-report)	HIV+ (blood test-confirmed) vs. general population	Smoking among HIV+ vs. HIV-, by 10-year age band	prevalence (20-29) = 23% vs. 35%; (30-39) 49% vs. 41%; (40-49) 50% vs. 39%; (50-59) 27% vs. 41%; (60-69) 20% vs. 24%	unadjusted
18	Petoumenos et al. (2017)	Australia	55yo+ HIV-, (n=218) and HIV+ (n=228) MSM	Clinic-based	Cross-sectional	Smoking (self-report: current vs. prior vs. none)	HIV status (blood test)	Smoking among HIV+ vs. HIV-	11.2 vs. 11.3%; p=0.081	age, smoking status, BMI
19	Pollack et al. (2017)	Hanoi, Vietnam	HIV+ individuals initiating ART (n=636)	Clinic-based	Cross-sectional (baseline assessments from longitudinal study)	Smoking past 30 days (self-report: 0 cigs/day, ≤10, >10)	Low VL <10 <sup>5</sup> copies/ml (blood test)	Low VL among <10 vs. 0 cigs/day; among >10 vs. 0 cigs/day <sup>†</sup>	adjusted OR = 0.50 (0.29, 0.87); adjusted OR = 0.71 (0.38, 2.00)	age, gender, body weight, alcohol, TB history, CD4, HIV
20	Shiau et al. (2017)	United States	General population (n=377787)	Population-based	Cross-sectional	Cigarette smoking, past month (self-report)	HIV status (self-report: lifetime diagnosis)	Cigarette smoking among HIV+ vs. HIV-	prevalence = 45.7% vs. 24.5%; p<0.001	sex, age, race/ethnicity, family income, marital status
21	Shokoohi et al. (2018)	Canada	HIV+ or HIV- women (n=46831)	Clinic-based (HIV+) and population-based (general population)	Cross-sectional	Smoking (self-report: daily vs. frequent vs. none)	HIV+ (blood test) vs. HIV- (general population)	Current smoking among HIV+ vs. HIV-	standardized prevalence = 43.7% vs. 17.8%; difference = 25.9% (22.9%, 28.9%)	age and ethnic group-standardized
								Daily smoking among HIV+ vs. HIV-	prevalence = 40.7% vs. 13.9%; difference = 26.8% (23.9%, 29.7%)	

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Smoking measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
22	Tron et al. (2014)	France	18-85yo HIV+ (n=3019) and general population controls (n=27653)	Clinic-based (HIV+) and population-based (general population)	Cross-sectional	Current smoking (self-report)	HIV+ (blood test) vs. HIV- (general population)	Regular smoking among HIV+ vs. HIV-	adjusted PRR (men) = 1.19 (0.98, 1.45); adjusted PRR (women) = 1.32 (1.10, 1.57)	age, education, age*education interaction
23	Zyambo et al. (2015)	Birmingham, United States	HIV+ patients in care (n=2464)	Clinic-based	Cross-sectional	Smoking (self-report: current vs. never)	ART adherence (self-report: 1 missed dose past month [AACTG])	Current smoking among ART adherent vs. non-adherent <sup>†</sup>	adjusted OR = 0.91 (0.63, 1.43)	age, gender/sexual orientation, race/ethnicity, ART adherence, comorbidities, VL, CD4, depression, anxiety, substance use
							CD4 (blood test: >350 vs. 200-350 vs. <200 cells/ul)	Current smoking among high vs. low CD4	adjusted OR = 0.8 (0.5, 1.2)	
							VL detectable (blood test: 50+ vs. <50 copies/ml)	Current smoking among undetectable vs. detectable VL <sup>†</sup>	adjusted OR = 0.67 (0.53, 0.91)	

Note: \* denotes studies that used cross-sectional data but the comparisons deemed relevant for this review were cross-sectional.

<sup>†</sup> denotes relationships that were transformed from the original study publication to facilitate comparison in this review.

Abbreviations: AACTG: Adult AIDS Clinical Trials Group, AIDS: Acquired Immune Deficiency Syndrome, ANC: Antenatal care, ART: Antiretroviral therapy, BMI: Body mass index, CO: Carbon monoxide, CVD: Cardiovascular disease, FSW: Female sex workers, HIV: Human immunodeficiency virus, IDU: Injection drug users, IeDEA: International Epidemiology Databases to Evaluate AIDS, MACS: Multicenter AIDS Cohort Study, MSM: Men who have sex with men, NHIS: National Health Interview Survey, OR: Odds ratio, PR: Prevalence ratio, RR: Risk ratio, SA NHANES: South Africa National Health and Nutrition Examination Survey, TB: Tuberculosis, VACS: Veterans Aging Cohort Study, VAS: Visual Analog Scale, VL: Viral load, VLS: Viral load suppression, WHO: World Health Organization, WIHS: Women's Interagency HIV Study

**Appendix Table 5.3 Cross-sectional analyses of alcohol use by HIV continuum stage**

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Alcohol measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
1	Allen et al. (2011)	Caribbean	HIV+ recipients of NGO services (n=394)	Convenience	Cross-sectional	Alcohol use past 12 months (self-report)	ART adherence >95%, past 12 months (self-report)	>95% ART adherence among alcohol users vs. non-users	adjusted OR = 0.47 (p=.039)	HIV disclosure, received HIV counseling, experienced ART side effects
2	Applebaum et al. (2009)	Boston, United States	HIV+ adults (n=67)	Clinic-based	Cross-sectional	Alcohol dependent (self-report: Addiction Severity Index-Lite)	% ART adherence, past 3 months (self-report)	% ART adherence among absence vs. presence of alcohol dependence	t-test = -2.315 (p<0.05) among women; NS among men	unadjusted
3	Aralis et al. (2018)	Los Angeles, United States	18-45yo HIV+ African American and Hispanic MSM (n=155)	Community-based	Cross-sectional	Hazardous alcohol use (AUDIT-C, self-report)	VLS (blood test)	VLS among hazardous alcohol use vs. others	adjusted $\beta$ = 0.34 (p=.449)	age, race/ethnicity
4	Chander et al. (2008)	United States	18+yo HIV+ pts enrolled in care (n=951)	Clinic-based	Cross-sectional	Hazardous vs. no alcohol use, past 4 weeks (self-report)	ART use vs. non-use (self-report)	Hazardous alcohol use among ART users vs. non-users	adjusted OR = 0.45 (0.23-0.86)	clinical site, demographics
							CD4 nadir >500 vs. <50 (self-report)	Hazardous alcohol use among CD4 nadir >500 vs. <50	adjusted OR = 2.65 (1.23-5.69)	
							Care visits attended, past 6 months (self-report)	Hazardous alcohol use among >8 vs. <3 visits attended	adjusted OR = 0.45 (0.23-0.86)	
5	Chersich et al. (2007)	Mombasa, Kenya	Female sex workers (n=719)	Community-based RDS	Cross-sectional	Alcohol users vs. non-users, past month (self-report)	HIV status (blood test)	Alcohol use among HIV+ vs. HIV-	adjusted prevalence = 39% vs. 23% (p<0.001)	alcohol frequency, age, education, religion, marital status, workplace, income
6	Cook et al. (2017)	Florida, United States	18+ yo HIV+ persons (n=619)	Community- and clinic-based	Cross-sectional	Alcohol use: heavy, binge, low, none (self-report: AUDIT-C)	>95% ART adherence (self-report)	ART adherent among non-drinkers vs. low vs. binge vs. heavy drinkers	Prevalence = 80% (no alc) vs. 68% (low) vs. 58% (binge) vs. 51% (heavy)	gender, education, homelessness, current smoking, illicit drug use, depressive symptoms, anxiety symptoms

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Alcohol measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
7	Cook et al. (2013)	United States	HIV+ women in care (n=2791)	Clinic-based (Women's Interagency HIV Study)	Cross-sectional (baseline assessments from longitudinal study)	Heavy drinking vs. none (self-report)	HIV status (blood test)	HIV status among heavy vs. non-drinkers	adjusted OR = 1.51 (1.00, 2.28)	age, race, marital status, education, employment, study recruitment site, period of enrollment, depressive symptoms, HCV status, other substance use, past drinking, past alcohol treatment
8	Crane et al. (2017)	United States	HIV+ patients in care at CNICS clinics (n=8567)	Clinic-based	Cross-sectional (most recent assessments from longitudinal study)	Hazardous alcohol use (self-report, AUDIT-C $\geq 5$ [men] or $\geq 4$ women out of 12)	VLS (blood test)	Hazardous alcohol use by VLS vs. not VLS: adjusted OR = 0.95 (0.81, 1.10)	adjusted OR = 0.95 (0.81, 1.10)	sex, age, race/ethnicity, HIV transmission risk factor,
							CD4 $\geq 350$ vs. $< 350$ (blood test)	Hazardous alcohol use among CD4 $\geq 350$ vs. $< 350$	adjusted OR = 1.16 (0.99, 1.34)	hepatitis C virus, depression, drug use, clinical site
9	da Silva et al. (2017)	Rio Grande, Brazil	18+ yo HIV+ patients in care (n=343)	Hospital-based	Cross-sectional	Alcohol use severity (4 levels), past year (self-report; AUDIT-C)	Length of HIV diagnosis (medical records)	Alcohol use severity per year since HIV diagnosis	adjusted PR = 1.00 (0.97, 1.03)	gender, skin color, education, income, STD, number of sexual partners, illicit drugs, hepatitis
							ART use vs. non-use (medical records)	Alcohol use severity by ART use vs. non-use	adjusted PR = 1.57 (0.79, 3.13)	
10	Do et al. (2013)	Multi-site, Vietnam	18-60yo HIV+ patients on ART (n=615)	Clinic-based	Cross-sectional	Heavy alcohol use (self-report: 5+ drinks at one time during the last month)	ART adherent (self-report: VAS and AACTG)	Optimal adherence among heavy alcohol use vs. less <sup>†</sup>	unadjusted OR = 0.51 (0.35, 0.74)	unadjusted
11	Elliott et al. (2016)	New York, United States	Injection and non-injection drug users receiving treatment (n=3305)	Clinic-based	Cross-sectional	Alcohol (self-report: drinkers vs. abstainers, past 6 mo)	HIV status (blood test)	Alcohol abstinence among HIV+ vs. HIV-	adjusted OR among IDUs = 1.04 (0.72, 1.51); among non-IDUs = 0.58 (0.41, 0.81)	age, sex, race, education

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Alcohol measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
12	Elul et al. (2013)	Rwanda	HIV+ adults on ART (n=1417)	Population-based	Cross-sectional	Alcohol use (self-report: any vs. none)	ART adherent, last 30 days (self-report)	Alcohol use among ART adherent vs. non-adherent <sup>†</sup>	adjusted OR = 0.65 (0.42, 0.99)	ART initiation, age, sex, CD4 at ART initiation, ART duration, ART side effects past 30 days, participation in PLWH association, facility characteristics
13	Etukumana et al. (2010)	Zawan, Nigeria	Pregnant women in ANC (n=350)	Clinic-based	Cross-sectional	Alcohol use, current (self-report)	HIV status (blood test)	HIV+ status among alcohol users vs. non-users	adjusted OR = 0.36 (0.04, 1.48)	not stated
14	Ferro et al. (2015)	Lima, Peru	HIV+ MSM and trans women in care (n=302)	Clinic-based	Cross-sectional	Alcohol use disorder (self-report: AUDIT $\geq$ 8 of 40)	>90% ART adherence (self-report: VAS)	ART adherent among alcohol use disorder vs. not AUD	adjusted OR = 0.43 (0.19, 0.98)	neurocognitive impairment, age, income, living alone, transgender women, employment, depression, drug use, domestic violence, HIV stigma, food insecurity
15	Ghebremichael et al. (2011)	Moshi, Tanzania	Men (n=567)	Population-based	Cross-sectional	Alcohol abuse (self-report; CAGE)	HIV-1 status (blood test)	Alcohol abuse among HIV+ vs. HIV-	prevalence = 48% vs. 36% ; $\chi^2=1.89$ (NS)	
16	Goulet et al. (2007)	United States	HIV+ (n=33,420) and HIV- (n=66,840)	Clinic-based (Veterans Aging Cohort Study Virtual Cohort)	Cross-sectional	Alcohol abuse and/or dependence (medical records: ICD-9)	HIV status (medical records: ICD-9)	Alcohol abuse or dependence among HIV+ vs. HIV- status	prevalence = 19% vs. 18%, t-test p<0.001	race, ethnicity, sex
17	Grierson et al. (2011)	Australia	HIV+ persons (n=1106)	Community-based	Cross-sectional	Alcohol use (self-report)	Difficulties with ART adherence (self-report)	No difficulties with ART adherence by alcohol use <sup>†</sup>	adjusted OR = 0.59 (0.38, 0.93)	age, urbanicity, health, self-rated health, ART dosing/regimen, adverse health events

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Alcohol measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
18	Ikeda et al. (2016)	Porto Alegre, Brazil	18+yo HIV+ patients in care (n=1240) and general population sample (n=1848)	Clinic-based (HIV+), population-based (general population)	Cross-sectional	Heavy alcohol use (self-report)	HIV+ (blood test) vs. HIV- (general population)	Heavy alcohol use among HIV+ vs. HIV-	prevalence = 5.6% vs. 10.3%; ANOVA p<0.001	sex, age, skin color, education, smoking
						Heavy episodic drinking (self-report: 5+ drinks in single occasion)		Heavy episodic drinking among HIV+ vs. HIV-	prevalence = 17.0% vs. 46.1%; ANOVA p<0.001	
19	Jaquet et al. (2010)	Benin, Cote d'Ivoire, Mali	HIV+ patients in care (n=2920)	Clinic-based	Cross-sectional	Hazardous alcohol use (self-report, AUDIT ≥8 of 40)	ART adherence ≥95%, past 4 days (self-report: ACTG questionnaire)	ART adherence among hazardous alcohol users vs. none <sup>†</sup>	adjusted OR = 0.21 (0.13, 0.38)	country, sex, age, formal education, marital status, CD4 count at ART initiation, history of adherence counseling
20	Kunzweiler et al. (2017)	Kenya	18+yo MSM not enrolled in HIV care (n=711)	Respondent-driven sampling	Cross-sectional (baseline assessments from longitudinal study)	Harmful alcohol use (self-report: AUDIT ≥8 of 40)	Previously diagnosed out-of-care vs. newly diagnosed vs. HIV- (blood test, self-report)	Previously diagnosed out-of-care (vs. HIV-) among non-harmful vs. harmful alcohol use	adjusted RR = 3.46 (1.63, 7.37)	age, education, MSM trauma, upsetting sexual experiences during childhood
								Newly diagnosed (vs. HIV-) among non-harmful vs. harmful alcohol use	adjusted RR = 1.13 (0.58, 2.22)	
21	Lancaster et al. (2016)	Lilongwe, Malawi	HIV+ female sex workers (n=138)	Venue-based	Cross-sectional	Harmful alcohol use (self-report: AUDIT ≥16 out of 20)	HIV awareness (blood test and self-report)	Unaware of HIV infection among harmful vs. nonharmful drinking	adjusted PR = 2.7 (1.0, 7.6)	duration in sex work (years), alcohol use prior to last vaginal sex with client and number of clients per week
22	Lancaster et al. (2017)	Lilongwe, Malawi	HIV+ female sex workers, previously diagnosed (n=111)	Venue-based	Cross-sectional	Harmful alcohol use (self-report: AUDIT ≥16 out of 20)	ART users vs. non-users (self-report)	ART use among harmful vs. nonharmful alcohol use <sup>†</sup>	adjusted PR = 0.53 (0.26, 1.00)	No. clients per week, housing, duration in sex work (years)
							VL suppression (blood test)	VL suppression among harmful vs. nonharmful alcohol use <sup>†</sup>	adjusted PR = 0.58 (0.18, 2.00)	
23	Magidson et al. (2017)	South Africa	18+yo HIV+ clinic patients on ART (n=101)	Clinic-based	Cross-sectional	Alcohol use (self-report: AUDIT ≥8 of 40)	ART non-adherent, past week (self-report: missed any dose)	ART adherence among alcohol users vs. non-users <sup>†</sup>	adjusted OR = 0.87 (0.78, 0.98)	demographics, depression, alcohol, stigma, CD4, VL

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Alcohol measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
24	Martinez et al. (2008)	Mbarara, Uganda	HIV+ patients in care (n=432)	Hospital-based	Cross-sectional	Alcohol use, past year (self-report)	ART use (self-report)	ART use among drinkers vs. non-drinkers <sup>†</sup>	adjusted OR = 0.44 (0.25, 0.77)	age, sex, income, education, illness, depressive symptoms, OIs
25	Medley et al. (2014)	Multi-country: Tanzania, Kenya, Namibia	HIV+ patients in care (n=3538)	Clinic-based	Cross-sectional (baseline assessment from longitudinal study)	Harmful drinking (self-report: AUDIT ≥8 of 40)	Time since diagnosis, <1 year vs. ≥3 years (self-report)	Harmful drinking among <1 year vs. ≥3 years since diagnosis	adjusted OR = 2.07 (1.32, 3.25)	country, demographics, HIV-related health, HIV risk behaviors
							ARV use (self-report)	Harmful drinking among ARV users vs. non-users <sup>†</sup>	adjusted OR = 0.73 (0.60, 0.88)	
26	Msuya et al. (2006)	Moshi, Tanzania	14+yo HIV+ pregnant women in ANC care (n=2654)	Clinic-based	Cross-sectional	Alcohol (self-report: daily vs. none)	HIV status (blood test)	HIV+ status among daily alcohol users vs. non-drinkers	adjusted OR = 1.70 (1.06, 2.67)	adjusted for demographic, partner characteristics, partner drinking
27	Nuken et al. (2013)	Nagalord, India	Female sex workers (n=417)	Community-based, respondent-driven sampling	Cross-sectional	Daily alcohol use (self-report)	HIV status (blood test)	Daily alcohol use among HIV+ vs. HIV-	prevalence = 30.2% vs. 18.0%	unadjusted
28	Pecoraro et al. (2015)	St. Petersburg, Russia	18+yo HIV+ pts non-adherent to ART (n=120)	Clinic-based	Cross-sectional	Alcohol use (self-report)	Lost to HIV care vs. engaged in care (self-report)	Engaged in HIV care among alcohol users vs. non-users <sup>†</sup>	prevalence = 32%; vs. 62%; adjusted OR = 0.36 (0.29, 0.46)	age, gender, race, sexual orientation, marital status, education, route of transmission
29	Petoumenos et al. (2017)	Australia	55yo+ HIV- (n=218), and HIV+ (n=228) MSM	Clinic-based	Cross-sectional	No. alcoholic drinks per week (self-report)	HIV status (blood test)	Drinks per week among HIV+ vs. HIV-	median drinks per week = 3 vs. 6; p=0.002	age, smoking status, BMI
30	Pollack et al. (2017)	Hanoi, Vietnam	HIV+ individuals initiating ART (n=636)	Clinic-based	Cross-sectional (baseline assessments from longitudinal study)	Binge drinking, past 30 days (self-report: binge vs. none)	High VL (blood test: >10 <sup>5</sup> vs. ≤10 <sup>5</sup> copies/ml)	High VL among binge vs. non-drinkers	adjusted OR = 0.66 (0.29, 1.50)	age, gender, body weight, alcohol, TB history, CD4, HIV

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Alcohol measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
31	Probst et al. (2017)	South Africa	South African general population (n=55144)	Population-based (South Africa NHANES)	Cross-sectional	Alcohol use, current (self-report: AUDIT)	HIV status (blood test)	HIV+ among current vs. non-drinker	adjusted RR = 0.53 (0.35, 0.81); in low SES stratum: adjusted RR = 2.37 (1.34, 4.18)	age, sex
32	Ramlagan et al. (2018)	Mpumalanga Province, South Africa	HIV+ pregnant women in antenatal care (n=673)	Clinic-based	Cross-sectional	Alcohol use, past 4 weeks (self-report: 2+ drinks vs. <2)	ART adherence (self-report: Visual Analog Scale [7 day recall] & AACTG measure [4 day recall])	ART adherence among drinkers vs. non-drinkers <sup>†</sup>	adjusted OR (AACTG measure) = 0.43 (0.26, 0.71); adjusted OR (VAS measure) = 0.49 (0.31, 0.79)	age, time on ARVs, desire to avoid side effects, HIV disclosure, knowledge, IPV, stigma, depression
33	Sacamano et al. (2016)	Baltimore, Maryland	HIV+ patients on ART (n=438)	Clinic-based	Cross-sectional	Excessive alcohol use, past 12 months (self-report)	Viral load <50 vs. ≥50 copies/ml (blood test)	VL undetectable among excessive alcohol users vs. others	adjusted PR = 0.83 (0.46, 1.49)	age, race, education, income, polysubstance use
34	Sarna et al. (2013)	Delhi, India	18+yo male IDUs (n=3792)	Respondent-driven sampling	Cross-sectional (baseline assessments from longitudinal study)	Alcohol use times per week (self-report: 0 vs. 1-2 vs. 3+)	HIV infection status (blood test)	HIV+ status among 1-2 vs. 0 alcohol use times/wk	adjusted OR (1-2 vs. 0) = 0.67 (0.55, 0.82); adjusted OR (3+ vs. 0) = 0.74 (0.54, 1.01)	age, education, marital status, religion, region of origin, accommodation, income, duration drug use, risky injection behavior, health service utilization, prior HIV testing, unsafe sex
35	Scott-Sheldon et al. (2013)	Cape Town, South Africa	General population (n=1717)	Convenience	Cross-sectional	Alcohol use, past month (self-report)	HIV status (self-report: lifetime diagnosis vs. negative/unknown status)	Alcohol use among HIV+ vs. HIV-	prevalence = 73% vs. 76% (p=0.034)	sex, age, ethnicity, education
						Drinking days, past month (self-report)		Drinking days among HIV+ vs. HIV- mediated via perceived stress	unstandardized coefficient = 0.68 (p<0.05)	
36	Sebit et al. (2003)	Epworth, Zimbabwe	18-55yo Epworth community residents (n=194)	Community- and household-based sampling	Cross-sectional	Alcohol use (self-report: AUDIT > 0)	HIV serostatus (blood test)	Drinking among HIV+ vs. HIV-	prevalence = 24.3% vs. 16.5% (p=0.415)	unadjusted

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Alcohol measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
37	Shaffer et al. (2004)	Moi, Kenya	Adults in HIV or primary care (n=299)	Clinic-based	Cross-sectional	Hazardous alcohol use (self-report: AUDIT >8 out of 40)	HIV+ (blood test-confirmed) vs. general medical clinic population	Hazardous alcohol use among HIV+ vs. general population	prevalence 68% vs. 46%; adjusted OR = 1.9 (1.1, 3.4)	sex, age
38	Shiau et al. (2017)	United States	General population (n=377787)	Population-based	Cross-sectional	Alcohol use past month (self-report)	HIV status (self-report: lifetime diagnosis)	Alcohol use among HIV+ vs. HIV-	prevalence = 61.9% vs. 55.8%; p=0.056	sex, age, race/ethnicity, family income, marital status
						Alcohol dependence (self-report)		Alcohol dependence among HIV+ vs. HIV-	prevalence = 6.1% vs. 3.4%; p=0.018	
39	Shokoohi et al. (2018)	Canada	HIV+ and general population women (n=46831)	Community-based (HIV+) and population-based (HIV-)	Cross-sectional	Alcohol use (self-report: none vs. <1 drink/wk, 2-3, 4+ in the last year)	HIV+ (blood test-confirmed) vs. general population	Alcohol among HIV+ vs. HIV-	prevalence = 59.3% vs. 72%; difference = -12.7% (-9.1%, 14.0%)	age and ethnic group-standardized
40	Sullivan et al. (2011)	United States	Veterans (n=2446)	Hospital-based (Veterans Aging Cohort Study)	Cross-sectional (baseline assessments from longitudinal study)	Alcohol use, unhealthy vs. low risk (clinical records and self-report: AUDIT >5 [women] or >7 [men] out of 12)	HIV infection status (clinical records, blood test)	HIV+ among unhealthy vs. low risk drinkers	prevalence = 52.1% vs. 55.9%; chi-squared p-value = 0.081	unadjusted
							>90% ART adherence, past year (clinical records)	ART adherent among unhealthy vs. low risk drinkers	prevalence = 19.2% vs. 23.0%; chi-squared p-value = 0.13	
							CD4 count (blood test)	CD4 count among unhealthy vs. low risk drinkers	mean (SD) = 419 (271) vs. 414 (269); p-value = 0.585	
							log(VL) (blood test)	log(VL) among unhealthy vs. low risk drinkers	mean (SD) = 3.1 (1.3) vs. 3.1 (1.3); p-value = 0.889	
41	Tran et al. (2013)	Vietnam	HIV+ patients on ART (n=1016)	Hospital-based	Cross-sectional	Alcohol use disorder (self-report: AUDIT-C >4 [men] or >3 [women] out of 12)	HIV stage (self-report: asymptomatic HIV vs. symptomatic HIV vs. AIDS)	HIV stage among AUD vs. no AUD	prevalence symptomatic HIV = 45.7% vs. 51.8%; prevalence AIDS = 42.2% vs. 35.6%; p-value = 0.13	socioeconomic status, HIV-related characteristics, service utilization variables
							ART use (self-report)	ART use among AUD vs. no AUD	prevalence = 85.0% vs. 90.4%; p-value = 0.01	

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Alcohol measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
							Length of HIV infection (self-report)	Length of HIV infection among AUD vs. no AUD	mean years = 5.4 vs. 5.4; p-value = 0.41	
42	Vagenas et al. (2014)	Peru	18yo+ HIV+ MSM in care (n=420)	Respondent-driven sampling, clinic-based	Cross-sectional	Alcohol use disorder (self-report: AUDIT 8+ out of 40)	HIV awareness (blood test and self-reported prior awareness)	Aware of HIV infection among AUD vs. no AUD <sup>†</sup>	adjusted OR = 0.47 (0.22, 0.99)	covariates not stated
43	Veld et al. (2017)	Pretoria, South Africa	HIV+ patients in primary care (n=2230)	Clinic-based	Cross-sectional	Hazardous alcohol use (self-report: AUDIT >7 [men] or >8 [women] out of 15)	≥95% ART adherence (self-report: VAS)	Hazardous alcohol use among ART adherent vs. non-adherent	adjusted OR = 0.53 (0.41, 0.69)	age, marital status, education, source of household income, HIV-related variables, other health variables, health-related quality of life, depressive symptoms, stigma
							Undetectable VL (measure not described)	Hazardous alcohol use among undetectable vs. detectable VL <sup>†</sup>	unadjusted OR = 0.61 (0.44, 0.84)	
44	Wandera et al. (2015)	Uganda	18yo+ HIV+ patients in care (n=725)	Hospital-based	Cross-sectional	Hazardous alcohol use, past 6 months (self-report: AUDIT-C >3 out of 12)	HIV clinical stage (clinical records: WHO stage III/IV vs. I/II) <sup>†</sup>	Hazardous alcohol use among HIV stage I/II vs. III/IV	unadjusted PR (men) = 0.72 (0.48, 1.08); (women) = 0.54 (0.33, 0.88)	unadjusted
							ART use (self-report)	Hazardous alcohol use among ART users vs. non-users <sup>†</sup>	adjusted PR (men) = 0.60 (0.37, 0.98); (women) = 0.56 (0.34, 0.91)	
45	Yaya et al. (2014)	Sokode, Togo	HIV+ on ART ≥3 mo (n=291)	Hospital-based	Cross-sectional	Alcohol use (self-report)	ART adherence (composite measure using self-report, appointment and pill counts)	ART adherence among alcohol users vs. non-users	prevalence = 60.3% vs. 83.9%; adjusted OR = 0.43 (0.20, 0.93)	education, CD4 count, ART perception, HIV disclosure, knowledge of partner's HIV status

Note: <sup>†</sup> denotes relationships that were transformed from the original study publication to facilitate comparison in this review.

**Appendix Table 5.4 Cross-sectional analyses of dietary behavior by HIV continuum stage**

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Dietary behavior measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
(none)										

**Appendix Table 5.5 Cross-sectional analyses of sedentary behavior by HIV continuum stage**

No.	Author(s) (year)	Location	Population (n)	Sampling	Study design	Sedentary behavior measure(s)	HIV continuum stage measure(s)	Comparison	Results	Covariates adjusted
1	Allen et al. (2011)	Caribbean	HIV+ recipients of NGO services (n=394)	Convenience	Cross-sectional	Exercise program participation, past 12 months (self-report)	>95% ART adherence, past 12 months (self-report)	No participation in exercise program among ART adherent vs. non-adherent <sup>†</sup>	unadjusted OR = 0.33 (p=.007)	HIV disclosure, HIV counseling, ART side effects
2	Gutierrez et al. (2013)	United States	20-49yo HIV+ (n=76) and HIV- adults (n=12263)	Population-based survey (NHANES)	Cross-sectional	Physical inactivity, past 30 days (self-report)	HIV status (blood test or self-reported ARV use)	Physical inactivity among HIV+ vs. HIV-	adjusted OR = 1.6 (0.8, 3.2)	sex, ethnicity, educational attainment, family income
3	Petoumenos et al. (2017)	Australia	55yo+ HIV-, (n=218) and HIV+ (n=228) MSM	Clinic-based	Cross-sectional	Hours exercise per week, walking / moderate / vigorous (self-report)	HIV status (blood test)	Exercise level among HIV+ vs. HIV-	t-test = NS (all measures)	age, smoking status, BMI
4	Silveira et al. (2018)	Goiás, Brazil	19+yo HIV+ patients in care (n=288)	Hospital-based	Cross-sectional	Physical inactivity (self-report: IPAQ <600 MET minutes/wk)	Time since diagnosis, >3 vs. 1-3 yrs (self-report)	Physical inactivity among >3 vs. 1-3 yrs since diagnosis	adjusted PR = 1.29 (0.95, 1.76)	age group, education, waist circumference, WHR, hypertension, diabetes
							ART use (self-report)	Physical inactivity among ART users vs. non-users	adjusted PR = 1.11 (0.83, 1.48)	
5	Stein et al. (2012)	Berlin, Germany	18yo+ HIV+ (n=124) and HIV- (n=159) patients in care	Hospital-based	Cross-sectional	Sports activity (self-report)	HIV status (self-report)	No sports activity among HIV+ vs. HIV- <sup>†</sup>	prevalence = 38.7% vs. 25.8%; Mann-Whitney p-value = 0.028; adjusted OR = 1.92	age, gender, sexual orientation, IDU

Note: <sup>†</sup> denotes relationships that were transformed from the original study publication to facilitate comparison in this review.

**Appendix Table 5.6 Summary of systematic review findings**

	CVD risk behavior			
	Smoking	Alcohol use	Poor diet	Sedentary
<b>HIV continuum stage</b>				
HIV infection	+(n=15)	<b>M</b> (n=22)	No studies	<b>0</b> (n=2)
HIV awareness	+(n=5)	<b>M</b> (n=8)	No studies	+(n=2)
HIV treatment	<b>M</b> (n=10)	-(n=27)	No studies	-(n=2)
HIV immune/viral recovery	-(n=9)	-(n=15)	<b>0</b> (n=1)	No studies

Note: This table summarizes the findings of the systematic review for each CVD risk behavior by HIV continuum stage comparison. Effect estimates were harmonized across studies to enable comparisons (i.e., associations were reversed if variables were reverse-coded in a given study). Symbols denote predominant direction of association observed for all studies included in each cell: + = predominantly positive; - = predominantly negative; **0** = predominantly null; **M** = overall mixed findings.

### Appendix Table 5.7 AUDIT-C questionnaire for hazardous alcohol use

The table below contains a side-by-side comparison of alcohol use questions from the original 3-item AUDIT-C questionnaire and corresponding questions from the HAALSI study that will be used to approximate the AUDIT-C score. Points for each response option are in parentheses, and scoring method follows the table.

Original AUDIT-C questions	Corresponding HAALSI survey questions
<p>1. <i>How often do you have a drink containing alcohol?</i></p> <ul style="list-style-type: none"> <li>a. <i>Never</i> (0 pts)</li> <li>b. <i>Monthly or less</i> (1 pt)</li> <li>c. <i>2-4 times a month</i> (2 pts)</li> <li>d. <i>2-3 times a week</i> (3 pts)</li> <li>e. <i>4 or more times a week</i> (4 pts)</li> </ul> <p>2. <i>How many standard drinks containing alcohol do you have on a typical day?</i></p> <ul style="list-style-type: none"> <li>a. <i>1 or 2</i> (0 pts)</li> <li>b. <i>3 or 4</i> (1 pt)</li> <li>c. <i>5 or 6</i> (2 pts)</li> <li>d. <i>7 to 9</i> (3 pts)</li> <li>e. <i>10 or more</i> (4 pts)</li> </ul> <p>3. <i>How often do you have six or more drinks on a single occasion?</i></p> <ul style="list-style-type: none"> <li>a. <i>Never</i> (0 pts)</li> <li>b. <i>Less than monthly</i> (1 pt)</li> <li>c. <i>Monthly</i> (2 pts)</li> <li>d. <i>Weekly</i> (3 pts)</li> <li>e. <i>Daily or almost daily</i> (4 pts)</li> </ul>	<p>0. <i>Do you currently (or in the last 30 days) consume any alcoholic drinks such as beer, wine, spirits, fermented cider, thothotho or traditional beer?</i></p> <ul style="list-style-type: none"> <li>a. <i>Yes</i> (proceed to next question)</li> <li>b. <i>No</i> (0 pts, skip to question 3)</li> </ul> <p>1. <i>How often do you have at least one alcohol drink?</i></p> <ul style="list-style-type: none"> <li>a. <i>Less than once per month</i> (1 pt)</li> <li>b. <i>1-3 days per month</i> (2 pts)</li> <li>c. <i>1-4 days per week</i> (3 pts)</li> <li>d. <i>5-6 days per week</i> (4 pts)</li> <li>e. <i>Daily</i> (4 pts)</li> </ul> <p>2. <i>On days you drink, how many alcoholic drinks do you have?</i></p> <ul style="list-style-type: none"> <li>a. <i>Less than 1</i> (0 pts)</li> <li>b. <i>1-2</i> (0 pts)</li> <li>c. <i>3-4</i> (1 pt)</li> <li>d. <i>5 or more</i> (2 pts)</li> </ul> <p>3. <i>In the past year, did you ever take 6 or more drinks in a single morning, afternoon or night?</i></p> <ul style="list-style-type: none"> <li>a. <i>Yes</i> (1 pt)</li> <li>b. <i>No</i> (0 pts)</li> </ul>

**Scoring:** Total score is calculated as the sum of points for all questions (out of 12 maximum points for original AUDIT-C, or 7 maximum points for HAALSI). As in the original AUDIT-C, hazardous alcohol consumption is defined as 4 or more points for men and 3 or more for women (see Bush et al., 1998). In order to approximate the AUDIT-C using the HAALSI baseline questionnaire, the questions most closely resembling those in the original were chosen. Since the range of responses for HAALSI questions 2 & 3 reflect a lower maximum severity of alcohol use, hazardous alcohol consumption may be underestimated among the most heavy drinkers, those who typically drink 7 or more drinks at a time or binge drink at least once per month.

## Appendix Table 5.8 IPAQ scoring for physical activity

Please consider your activity during a usual week. Think first about the time you spend doing work. Think of work as the things that you have to do such as paid or unpaid work, study/training, household chores, harvesting food/crops, fishing or hunting for food, seeking employment. In the following questions 'vigorous-intensity activities' are activities that require hard physical effort and cause large increases in breathing or heart rate, 'moderate-intensity activities' are activities that require moderate physical effort and cause small increases in breathing or heart rate.

1. Does your work involve mostly sitting or standing still, or walking for very short periods (less than 10 minutes)?
  - a. Yes (skip to question 4a)
  - b. No (proceed)
- 2a. Does your work involve vigorous activities (heavy lifting, digging, manual labour or construction) for at least 10 minutes at a time?
  - a. Yes (proceed)
  - b. No (skip to question 3a)
- 2b. In a usual week, how many days are spent doing vigorous activities as part of your work? On a usual day of vigorous work, how many hours are spent doing these activities?  
\_\_\_ Days      \_\_\_ Hours      \_\_\_ Minutes
- 3a. Does your work involve moderate-intensity activities (brisk walking or carrying light loads) for at least 10 minutes at a time?
  - a. Yes (proceed)
  - b. No (skip to question 4a)
- 3b. In a usual week, how many days are spent doing moderate-intensity activities as part of your work? On a usual work day, how many hours are spent doing moderate-intensity activities?  
\_\_\_ Days      \_\_\_ Hours      \_\_\_ Minutes

Please consider your activity during a usual week. These questions exclude the physical activities at work that you have already mentioned. These questions are about the usual way you travel to and from places. For example to work, for shopping, to market, to place of worship.

- 4a. Do you walk or use a bicycle (for at least 10 minutes at a time) to get to and from places?
  - a. Yes (proceed)
  - b. No (skip to question 5)
- 4b. In a usual week, how many days do you walk or cycle for at least 10 minutes to get to and from places? On a usual day, how many hours do you spend walking or cycling for travel?  
\_\_\_ Days      \_\_\_ Hours      \_\_\_ Minutes  
Please consider your activity during a usual week. The next questions, exclude the work and transport activities that you have already mentioned, they are about sports, fitness and recreational activities (leisure).
5. In your spare time, do you engage in any vigorous or moderate-intensity physical activities lasting more than 10 minutes at a time?
  - a. Yes (end)
  - b. No (proceed)
- 6a. In your spare time do you do any vigorous activities like running, strenuous sport or exercise for at least 10 minutes at a time?
  - a. Yes (proceed)
  - b. No (skip to question 7a)
- 6b. In a usual week, how many days do you engage in vigorous activities as part of your leisure time? In a normal day, how many leisure hours are spent doing vigorous activities?  
\_\_\_ Days      \_\_\_ Hours      \_\_\_ Minutes
- 7a. In your spare time, do you engage in any moderately intense physical activities like walking or swimming for at least 10 minutes at a time?
  - a. Yes (end)
  - b. No (proceed)
- 7b. In a normal week, how many days are spent engaging in moderately intense physical activity as part of your leisure time? How many leisure hours are spent doing moderate-intensity activities in a normal day?  
\_\_\_ Days      \_\_\_ Hours      \_\_\_ Minutes

**Scoring:** Guidelines for using the International Physical Activity Questionnaire (IPAQ) define three categories of physical activity, which signify ‘total physical activity level’ inclusive of recreational as well as daily living and work-related activity (see Lee et al., 2011), as opposed to recreational only. This measure has been validated in sub-Saharan African settings (see Oyeyemi et al., 2014):

**Insufficiently active (Category 1)**

Individuals who do not meet criteria for Categories 2 or 3

**Minimally active (Category 2)**

Individuals who meet any one of the following criteria but do not meet criteria for Category 3:

- a) 3 or more days of vigorous activity of at least 20 minutes per day OR
- b) 5 or more days of moderate-intensity activity or walking of at least 30 minutes per day OR
- c) 5 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 600 MET-min/week

**Health-enhancing physical activity (HEPA) (Category 3)**

Individuals who meet any one of the following criteria:

- a) vigorous-intensity activity on at least 3 days achieving a minimum of at least 1500 MET-minutes/week OR
- b) 7 or more days of any combination of walking, moderate-intensity or vigorous intensity activities achieving a minimum of at least 3000 MET-minutes/week

Total MET-minutes/week ( $\varphi$ ) is calculated using the following formula:

$$\varphi = (3.3 \text{ METs} \times \text{days}_{\text{walk}} \times \text{min}_{\text{walk}}) + (4.0 \text{ METs} \times \text{days}_{\text{moderate}} \times \text{min}_{\text{moderate}}) + (8.0 \text{ METs} \times \text{days}_{\text{vigorous}} \times \text{min}_{\text{vigorous}})$$

**Appendix Table 5.9 Measures of physiological and psychological HIV-related stress**

Survey question	Question text	Response options
<b>CD</b>	<b>Depressive symptoms (CESD-8)</b> Now think about the past week and the feelings you have experienced. Please tell me if each of the following was true for you much of the time this past week. Would you say yes or no?	
CD001	Much of the time in the past week, you felt depressed	Yes/No
CD002	Much of the time in the past week, you felt that everything you did was an effort.	Yes/No
CD003	Much of the time in the past week, your sleep was restless.	Yes/No
CD004	Much of the time in the past week, you were happy.	Yes/No
CD005	Much of the time in the past week, you felt lonely.	Yes/No
CD006	Much of the time in the past week, you did not enjoy life.	Yes/No
CD007	Much of the time in the past week, you felt sad.	Yes/No
CD008	Much of the time in the past week, you could not get "going".	Yes/No
<b>SW</b>	<b>Subjective well-being (from Gallup World Poll)</b>	
SW001	(Life satisfaction) All things considered, how satisfied are you with your life as a whole these days? Use a 0 to 10 scale, where 0 is dissatisfied and 10 is satisfied.	Numeric (0-10)
SW013	(Global life evaluation) Please imagine a ladder with steps numbered from 0 at the bottom to 10 at the top. Suppose we say that the top of the ladder represents the best possible life for you and the bottom of the ladder represents the worst possible life for you. On which step of the ladder would you say you personally feel you stand at this time, assuming that the higher the step the better you feel about your life, and the lower the step the worse you feel about it? Which step comes closest to the way you feel?	Numeric (0-10)
<b>PT</b>	<b>Performance tests (Hand grip strength test)</b>	
PT043	Grip strength first LEFT	Numeric (0-50 kg)
PT044	Grip strength second LEFT	Numeric (0-50 kg)
PT045	Grip strength first RIGHT	Numeric (0-50 kg)
PT046	Grip strength second RIGHT	Numeric (0-50 kg)
<b>PN</b>	<b>Pain (Brief Pain Inventory)</b>	
	(Pain severity) On a scale of 0 to 10, where 0 is "No pain" and 10 is "Pain as bad as you can imagine", please rate your pain...	
PN003	... at its worst in the last 24 hours.	Numeric (0-10)
PN004	... at its least in the last 24 hours.	Numeric (0-10)
PN005	... on average.	Numeric (0-10)
PN006	... how much pain you have right now.	Numeric (0-10)
	(Pain interference) On a scale of 0 to 10, where 0 is "Does not interfere" and 10 is "Completely interferes", select the one number that describes how, during the past 24 hours, pain has interfered with your ...	
PN009	... general activity.	Numeric (0-10)
PN010	... mood.	Numeric (0-10)

PN011	... walking ability.	Numeric (0-10)
PN012	... normal work (includes both work outside the home and housework).	Numeric (0-10)
PN013	... relations with other people.	Numeric (0-10)
PN014	... sleep.	Numeric (0-10)
PN015	... enjoyment of life.	Numeric (0-10)
<b>CN</b>	<b>Cognitive difficulties</b>	
CN001	How would you rate your memory at the present time?	Excellent/Very good/Good/ Fair/Poor
CN002	Overall in the last 30 days, how much difficulty did you have with concentrating or remembering things?	None/Mild/Moderate/ Severe/Extreme/cannot do
CN003	Overall in the last 30 days, how much difficulty did you have in learning a new task (for example, learning how to get to a new place, learning a new game, learning a new recipe)?	None/Mild/Moderate/ Severe/Extreme or cannot do
<b>PF</b>	<b>Difficulties with ADLs (Katz Index of Independence in Activities of Daily Living)</b>	
	We need to understand difficulties people may have with various activities because of a health or physical problem. Please tell me whether you have difficulty performing any of the following tasks on a regular basis. Exclude any difficulties that you expect to last less than three months. Because of health and memory problems, do you have any difficulty with ...	
PF001	... walking across a room?	Yes/No/Can't do/Don't want to
PF002	(if yes) ... Do you ever use equipment or devices when crossing a room?	Yes/No
PF004	(if yes) ... Does anyone ever help you get across a room?	Yes/No
PF005	... dressing? Dressing includes taking clothes out, putting them on, buttoning up, and fastening a belt.	Yes/No/Can't do/Don't want to
PF006	(if yes) ... Do you ever use equipment or devices when dressing?	Yes/No
PF008	(if yes) ... Does anyone ever help you with dressing?	Yes/No
PF009	... bathing or showering?	Yes/No/Can't do/Don't want to
PF010	(if yes) ... Do you ever use equipment or devices when bathing or showering?	Yes/No
PF012	(if yes) ... Does anyone ever help you with bathing or showering?	Yes/No
PF013	... eating, such as cutting up your food? (Definition: By eating, we mean eating food by oneself when it is ready.)	Yes/No/Can't do/Don't want to
PF014	(if yes) ... Does anyone ever help you with eating?	Yes/No
PF015	... getting into or out of the place where you sleep?	Yes/No/Can't do/Don't want to
PF016	(if yes) ... Do you ever use equipment or devices when getting into or out of the place where you sleep?	Yes/No
PF018	(if yes) ... Does anyone ever help you with getting into or out of the place where you sleep?	Yes/No
PF019	... using the toilet, including getting up and down?	Yes/No/Can't do/Don't want to
PF020	(if yes) ... Do you ever use equipment or devices when using the toilet?	Yes/No
PF022	(if yes) ... Does anyone ever help you with using the toilet?	Yes/No

**Appendix Table 5.10 Bivariate associations between hypothesized confounders and exposure and outcome variables**

Potential confounder	Exposure categories (HIV continuum stage)			Outcomes (CVD risk behaviors)		
	HIV+ unaware	HIV+ aware untreated	HIV+ on treatment	Smoking	Alcohol	Sedentary behavior
	PR (90% CI)	PR (90% CI)	PR (90% CI)	PR (90% CI)	PR (90% CI)	PR (90% CI)
<b>Demographics</b>						
Male	<b>0.80 (0.65, 0.99)</b>	0.88 (0.62, 1.25)	1.03 (0.89, 1.18)	<b>52.15 (27.93, 97.36)</b>	<b>3.54 (2.90, 4.33)</b>	0.95 (0.89, 1.01)
Age	<b>0.94 (0.93, 0.95)</b>	<b>0.93 (0.91, 0.95)</b>	<b>0.95 (0.94, 0.95)</b>	<b>0.97 (0.96, 0.98)</b>	1.00 (0.99, 1.00)	<b>1.02 (1.02, 1.02)</b>
Education	<b>1.43 (1.13, 1.83)</b>	<b>2.29 (1.59, 3.31)</b>	<b>1.41 (1.19, 1.67)</b>	1.14 (0.93, 1.41)	<b>0.61 (0.47, 0.79)</b>	<b>0.76 (0.70, 0.83)</b>
Employment	<b>1.75 (1.36, 2.24)</b>	1.29 (0.82, 2.02)	<b>1.55 (1.30, 1.86)</b>	<b>1.40 (1.13, 1.72)</b>	0.98 (0.77, 1.24)	<b>0.65 (0.59, 0.72)</b>
Married	<b>0.47 (0.38, 0.59)</b>	<b>0.57 (0.40, 0.81)</b>	<b>0.52 (0.45, 0.60)</b>	0.98 (0.82, 1.16)	1.09 (0.92, 1.29)	<b>0.86 (0.81, 0.91)</b>
Poorest 40%	<b>1.31 (1.06, 1.61)</b>	1.20 (0.85, 1.70)	<b>1.23 (1.07, 1.42)</b>	<b>1.59 (1.34, 1.90)</b>	<b>2.28 (1.92, 2.72)</b>	1.03 (0.97, 1.10)
<b>CVD history</b>						
Hypertension	<b>0.52 (0.42, 0.66)</b>	0.72 (0.50, 1.03)	<b>0.60 (0.52, 0.70)</b>	<b>0.36 (0.29, 0.44)</b>	<b>0.55 (0.45, 0.66)</b>	<b>1.25 (1.18, 1.33)</b>
Dyslipidemia/heart disease	<b>0.63 (0.44, 0.90)</b>	0.62 (0.33, 1.14)	0.90 (0.72, 1.12)	<b>0.57 (0.41, 0.79)</b>	<b>0.64 (0.47, 0.88)</b>	0.98 (0.90, 1.07)
Diabetes	<b>0.53 (0.31, 0.89)</b>	0.72 (0.34, 1.55)	<b>0.65 (0.47, 0.90)</b>	<b>0.27 (0.14, 0.51)</b>	<b>0.17 (0.08, 0.38)</b>	<b>1.25 (1.14, 1.38)</b>

Note: bolded variables met  $p < 0.10$  criterion for selection as potential confounder for adjustment

**Appendix Table 5.11 Predicted prevalence of CVD risk behaviors by HIV continuum stage overall, and stratified by sex**

	<b>Tobacco smoking</b>	<b>Hazardous alcohol use</b>	<b>Sedentary behavior</b>
	Prevalence <sup>1</sup> (95% CI)	Prevalence (95% CI)	Prevalence (95% CI)
<b>Overall (n=4,061)</b>			
<b>HIV continuum stage</b>			
HIV–	9.3% (8.3%, 10.4%)	9.7% (8.7%, 10.8%)	43.1% (41.3%, 44.8%)
HIV+ unaware	7.9% (5.2%, 10.7%)	10.2% (6.9%, 13.4%)	47.4% (40.9%, 53.8%)
HIV+ aware untreated	10.6% (5.1%, 16.0%)	10.8% (4.6%, 16.9%)	39.7% (29.1%, 50.3%)
HIV+ on treatment	8.8% (6.8%, 10.8%)	8.1% (6.1%, 10.2%)	38.8% (34.7%, 42.9%)
<b>Males (n=1,858)</b>			
<b>HIV continuum stage</b>			
HIV–	19.9% (17.7%, 22.0%)	16.2% (14.3%, 18.2%)	42.0% (39.5%, 44.6%)
HIV+ unaware	17.8% (12.2%, 23.4%)	17.6% (11.9%, 23.3%)	43.5% (33.3%, 53.8%)
HIV+ aware untreated	22.2% (12.1%, 32.3%)	12.5% (3.4%, 21.6%)	39.1% (22.8%, 55.5%)
HIV+ on treatment	19.0% (15.1%, 23.0%)	12.8% (9.2%, 16.3%)	39.4% (33.6%, 45.2%)
<b>Females (n=2,203)</b>			
<b>HIV continuum stage</b>			
HIV–	0.3% (0.0%, 0.6%)	4.2% (3.2%, 5.1%)	43.9% (41.6%, 46.3%)
HIV+ unaware	0.0% (0.0%, 0.0%)	4.0% (0.9%, 7.2%)	49.9% (41.5%, 58.2%)
HIV+ aware untreated	0.0% (0.0%, 0.0%)	11.4% (1.0%, 21.8%)	40.5% (26.4%, 54.6%)
HIV+ on treatment	0.5% (0.0%, 1.3%)	4.7% (2.2%, 7.2%)	38.1% (32.4%, 43.8%)

<sup>1</sup> Prevalence was estimated using log-poisson regression with robust SEs, adjusted for adjusted for sex, age, education (at least primary), employed (full or part-time), married, wealth index (poorest 40% vs. richest 60%), hypertension, dyslipidemia, diabetes and overweight (BMI>25).

**Appendix Table 5.12 Comparison of complete case sample and multiple imputation (MI) sample**

Variable	Complete cases n=4,061 n (%)	MI sample n=4,610 n (%)	n (%) missing
<b>Demographics</b>			
Male	1,858 (46%)	2,122 (46%)	0 (0.0%)
Age group			0 (0.0%)
40-49	767 (19%)	827 (18%)	
50-59	1,177 (29%)	1,287 (28%)	
60-69	1,099 (27%)	1,213 (26%)	
70+	1,018 (25%)	1,283 (28%)	
Completed primary education	826 (20%)	892 (19%)	14 (0.3%)
Employed (full or part-time)	669 (16%)	731 (16%)	10 (0.2%)
Married	2,142 (53%)	2,373 (52%)	3 (0.1%)
Poorest 40% <sup>1</sup>	1,623 (40%)	1,889 (41%)	0 (0.0%)
<b>HIV-related</b>			
HIV continuum stage			0 (0.0%)
HIV–	3,038 (75%)	3,478 (76%)	
HIV+ unaware	275 (7%)	302 (7%)	
HIV+ aware untreated	93 (2%)	104 (2%)	
HIV+ on treatment	655 (16%)	726 (15%)	
Virally suppressed (among HIV+)	513 (54%)	568 (54%)	4 (0.4%)
<b>CVD risk behaviors</b>			
Tobacco smoking <sup>2</sup>	371 (9%)	416 (9%)	3 (0.1%)
Hazardous alcohol use <sup>3</sup>	386 (10%)	444 (10%)	2 (0.0%)
Sedentary behavior <sup>4</sup>	1,731 (43%)	2,120 (47%)	0 (0.0%)
<b>CVD history</b>			
Hypertension	1,725 (42%)	1,975 (43%)	2 (0.0%)
Dyslipidemia or heart disease	513 (13%)	588 (13%)	22 (0.5%)
Diabetes	270 (7%)	325 (7%)	1 (0.0%)
<b>Physiological symptoms</b>			
Muscle weakness	2,660 (66%)	2,939 (64%)	214 (4.6%)
Pain	343 (8%)	409 (9%)	86 (1.9%)
Cognitive difficulties (memory/concentration/learning)	1,711 (42%)	2,005 (44%)	83 (1.8%)
Physical dysfunction (difficulties with ADLs)	353 (9%)	562 (12%)	0 (0.0%)
<b>Psychological symptoms</b>			
Depressive symptoms (CESD-8 score 5+ out of 8)	318 (8%)	395 (9%)	79 (1.7%)
Low subjective well-being	1,163 (29%)	1,335 (29%)	143 (3.1%)

<sup>1</sup> Based on household wealth index.

<sup>2</sup> Self-reported current use of smoking tobacco (cigarettes, cigars or pipes).

<sup>3</sup> AUDIT-C score >4 for men, >3 for women out of 7 total points.

<sup>4</sup> Does not meet criteria for minimal physical activity using IPAQ scoring.

**Appendix Table 5.13 Comparison of complete case sample and full baseline cohort**

Variable	Complete cases n=4,061 n (%)	Full cohort n=5,059 n (%)	n (%) missing	$\chi^2$
<b>Demographics</b>				
Male	1,858 (46%)	2,345 (46%)	0 (0.0%)	0.20
Age group			0 (0.0%)	<0.01
40-49	767 (19%)	918 (18%)		
50-59	1,177 (29%)	1,410 (28%)		
60-69	1,099 (27%)	1,304 (26%)		
70+	1,018 (25%)	1,427 (28%)		
Completed primary education	826 (20%)	1,020 (20%)	17 (0.3%)	<0.01
Employed (full or part-time)	669 (16%)	805 (16%)	14 (0.3%)	<0.01
Married	2,142 (53%)	2,575 (51%)	4 (0.1%)	<0.01
Poorest 40% <sup>1</sup>	1,623 (40%)	2,047 (41%)	0 (0.0%)	<0.01
<b>HIV-related</b>				
HIV continuum stage			449 (8.9%)	<0.01
HIV-	3,038 (75%)	3,478 (76%)		
HIV+ unaware	275 (7%)	302 (7%)		
HIV+ aware untreated	93 (2%)	104 (2%)		
HIV+ on treatment	655 (16%)	726 (15%)		
Virally suppressed (among HIV+)	513 (54%)	556 (53%)	4 (0.4%)	0.09
<b>CVD risk behaviors</b>				
Tobacco smoking <sup>2</sup>	371 (9%)	460 (9%)	5 (0.1%)	<0.01
Hazardous alcohol use <sup>3</sup>	386 (10%)	479 (9%)	4 (0.1%)	<0.01
Sedentary behavior <sup>4</sup>	1,731 (43%)	2,372 (47%)	1 (0.0%)	<0.01
<b>CVD history</b>				
Hypertension	1,725 (42%)	2,118 (42%)	4 (0.1%)	<0.01
Dyslipidemia or heart disease	513 (13%)	641 (13%)	24 (0.5%)	<0.01
Diabetes	270 (7%)	352 (7%)	4 (0.1%)	<0.01
<b>Physiological stress</b>				
Muscle weakness	2,660 (66%)	3,145 (67%)	360 (7.1%)	<0.01
Pain	343 (8%)	439 (9%)	117 (2.3%)	<0.01
Cognitive difficulties (memory/concentration/learning)	1,711 (42%)	2,223 (45%)	119 (1.8%)	<0.01
Physical dysfunction (difficulties with ADLs)	353 (9%)	634 (13%)	0 (0.0%)	<0.01
<b>Psychological stress</b>				
Depressive symptoms (CESD-8 score 5+ out of 8)	318 (8%)	442 (9%)	108 (2.1%)	<0.01
Low subjective well-being	1,163 (29%)	1,458 (30%)	179 (3.4%)	<0.01

This table shows comparisons of observed data between the complete case sample and full baseline cohort.