RELATIONSHIP BETWEEN FOOD INSECURITY AND HIV OUTCOMES AMONG INDIVIDUALS RECEIVING ANTIRETROVIRAL THERAPY IN BRITISH COLUMBIA, CANADA

by

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ABSTRACT

**Background:** Little is known about the relationship between food insecurity and health outcomes among people living with HIV/AIDS. This dissertation therefore sought to: i) review global evidence regarding the associations between food insecurity and HIV outcomes; ii) assess the prevalence and correlates of food insecurity among HIV-positive individuals receiving antiretroviral therapy (ART) across British Columbia (BC); iii) examine the relationship between hunger and plasma HIV RNA suppression among illicit drug users receiving ART in Vancouver; and iv) investigate the potential impact of food insecurity on mortality among injection drug users (IDU) receiving ART in BC.

**Methods:** Adults receiving ART in three BC-based observational studies completed interviewer-administered surveys eliciting information about socio-demographic profile, risk behavior, and health status, and consenting to database linkage for retrieval of clinical, laboratory and prescription information. Explanatory, confounder and survival models were built to investigate the associations between food insecurity and ART outcomes.

**Results:** A growing body of literature suggests that food insecurity is associated with increased risk of HIV transmission, poor ART access, adherence, pharmacokinetic efficacy, immunologic and virologic response, and reduced survival (Chapter 2). In a sample of 457 individuals receiving ART across BC, food insecurity was reported by 71% and was independently associated with younger age, illicit drug use, low annual income, tobacco smoking and symptoms of depression in explanatory models (Chapter 3). Among 406 illicit drug users receiving ART in Vancouver, 63% reported hunger and 59% had suppressed viral loads. Hunger and virologic suppression were not
independently associated in multivariate confounder models (Chapter 4). Among 254 IDU receiving ART across BC, 41% died between June 1998 and September 2011. Food insecurity was associated with a two-fold increased risk of death in adjusted survival models (Chapter 5).

**Conclusion:** This dissertation reviewed current evidence and gaps in knowledge about the relationship between food insecurity and HIV outcomes. Empirical results suggest an urgent need for evidence-based social and structural interventions to reduce food insecurity and associated harms among HIV-infected individuals in BC, particularly among illicit drug users. Public health efforts should consider evaluating the possible role of nutritional supplementation within existing harm reduction and HIV services.
PREFACE

Empirical studies contained in this dissertation draw on data from observational studies. Ethics approval (H12-03050) was obtained from the Providence Health Care / University of British Columbia Research Ethics Board for analysis of secondary data within the Longitudinal Investigation into Supportive and Ancillary health Services study (H06-00265); the AIDS Care Cohort to Evaluate access to Survival Services (H05-50233), and the HIV/AIDS Drug Treatment Program (H05-50123).

Chapters and Appendices contained in this dissertation are presently in various stages of publication. A total of eight manuscripts have been developed from content in this dissertation. As of December 2012, four manuscripts have been published in peer reviewed scientific journals and four have been submitted to scientific journals for review. Details of these manuscripts, including the contributions of all co-authors, are described below.

Select sections from Chapter 1 have been incorporated into a manuscript that is currently under review at Food and Nutrition Bulletin. Sections from Chapter 1 included in this submitted manuscript describe inter-institutional definitions of food insecurity and its main sub-components (i.e. food insufficiency, poor dietary diversity and poor food safety); the relevance of food insecurity in the context of HIV; and international efforts aimed at harmonizing indicators for measurement of food insecurity in HIV-affected populations. AA conceived of, designed and wrote the first draft of the paper. Co-authors SJF, TC, AH, NG and MB contributed specialist knowledge in clinical nutrition and in multilateral and bilateral foreign aid policy. All authors approved the final version of the manuscript. Co-authors on this manuscript include senior officials from the United Nations World Food Program (WFP) and United States Agency for International Development (USAID), representing institutional endorsement of concepts described within:

Text in Chapter 1 describing the relevance of food insecurity among illicit drug users has been published in Substance Abuse Treatment, Prevention and Policy. AA conceived of the study, guided study analysis and wrote the first draft of the paper. JQ performed statistical analyses. WE, SDW, and SGM provided expert review. TK provided overall guidance and mentorship for the publication, as Principal Investigator of the study. All authors approved the final version of the manuscript.


An earlier version of Chapter 2 has been published in Current HIV/AIDS Reports. This manuscript describes current knowledge, gaps and research priorities pertaining to food insecurity and HIV/AIDS. AA conceived of, designed and drafted the manuscript. Co-authors NV, EF and SK reviewed and provided specialist feedback on drafts. SW mentored the research process, and contributed expert knowledge and strategic guidance. All authors approved the final version of the manuscript.


A modified version of Chapter 3 has been published in AIDS Care. This manuscript describes the prevalence and correlates of food insecurity in a sample of HIV-positive individuals receiving treatment. AA conceived, designed and wrote the first draft of this manuscript. SW contributed specialist knowledge and review. KF and ED conducted statistical analyses. EB and AP reviewed the manuscript for details regarding study
management. JM contributed clinical and epidemiologic review. RH provided overall strategic guidance and mentorship for the analysis, and was Principal Investigator of the study. All authors approved the final version of the manuscript.


An abbreviated version of Chapter 4 has been submitted to the *Harm Reduction Journal* for peer review and prospective publication. AA conceived of, performed statistical analyses for, and wrote the first draft of this manuscript. MJ and CF contributed statistical supervision and critical review. TK and JM provided feedback and guidance. EW provided overall strategic and methodological direction, as Principal Investigator of the study. All authors approved the final version of the manuscript.


An abbreviated version of Chapter 5 has been submitted for peer review and prospective publication to the *American Journal of Public Health*. AA conceived of, performed statistical analyses for, and wrote the first draft of, this manuscript. KC provided statistical supervision. TK, EW and JM provided critical review and feedback. RH contributed overall strategic guidance, as Principal Investigator of the study. All authors approved the final version of the manuscript:


A modified version of Appendix 1 has been published in the *European Infectious Diseases*. This paper reviews evidence of the role of highly active antiretroviral therapy
in reducing morbidity, mortality and population-level HIV transmission. AA conducted the literature review and wrote the first draft of the manuscript. VDL, KJ, AL contributed health economic and statistical analyses to the published manuscript (not included in this dissertation). JM conceived of the content of the paper, provided overall strategic guidance, and clinical and scientific review. All authors approved the final version of the manuscript.


Content from **Appendix 2** has been reworked into a methodological commentary that is currently under review by *BMC Medical Research Methodology*. AA conceived of the review and wrote the first draft. EK contributed knowledge about directed acyclic graphs. LM provided overall strategic guidance and contributed statistical expertise. All authors approved the final version of the manuscript.

TABLE OF CONTENTS

ABSTRACT ................................................................................................................................. ii
PREFACE...................................................................................................................................... iv
TABLE OF CONTENTS .................................................................................................................. viii
LIST OF TABLES .......................................................................................................................... xvi
LIST OF FIGURES ...................................................................................................................... xv
LIST OF ABBREVIATIONS ............................................................................................................ xvii
ACKNOWLEDGEMENTS ................................................................................................................ xx

CHAPTER 1: BACKGROUND, RATIONALE, OBJECTIVES ......................................................... 1

1.1 Synopsis ................................................................................................................................ 1
1.2 Global Overview of Food Insecurity and HIV ................................................................. 1
1.3 Inter-relationship Between Food Insecurity and HIV/AIDS ........................................... 3
1.4 Food Insecurity Among HIV-Positive Illicit Drug Users .............................................. 4
1.5 Conceptual Frameworks ..................................................................................................... 5
  1.5.1 Rhodes’ Risk Environment Framework ................................................................. 6
  1.5.2 World Food Program’s Dimensions of Food Security ......................................... 7
  1.5.3 Weiser’s Bi-directional Pathways Between Food Insecurity and HIV Outcomes ................................................................................................................................. 8
  1.5.4 Montaner’s HIV Treatment as Prevention ........................................................... 9
  1.5.5 Adapted Risk Environment Framework ............................................................... 10
1.6 Global and Local Gaps in Knowledge ............................................................................. 14
1.7 Study Objectives and Hypotheses .................................................................................... 16
1.8 Study Setting, Design and Methods .................................................................................. 18
  1.8.1 Longitudinal Investigation into Supportive and Ancillary health services (LISA) ................................................................................................................................. 18
  1.8.2 AIDS Care Cohort to Evaluate access to Survival Services (ACCESS) ................................................................. 19
  1.8.3 HIV/AIDS Drug Treatment Program (DTP) ....................................................... 120
1.9 Summary .............................................................................................................................. 21
### CHAPTER 2: IMPACT OF FOOD INSECURITY ON HIV OUTCOMES: A REVIEW OF CURRENT KNOWLEDGE, GAPS AND RESEARCH PRIORITIES

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Synopsis</td>
<td>22</td>
</tr>
<tr>
<td>2.2</td>
<td>Introduction</td>
<td>23</td>
</tr>
<tr>
<td>2.3</td>
<td>Methods</td>
<td>24</td>
</tr>
<tr>
<td>2.4</td>
<td>Results</td>
<td>25</td>
</tr>
<tr>
<td>2.4.1</td>
<td>Definitions and Sub-components of Food Insecurity</td>
<td>25</td>
</tr>
<tr>
<td>2.4.2</td>
<td>Measures and Indicators of Food Insecurity Among HIV-positive Individuals</td>
<td>29</td>
</tr>
<tr>
<td>2.4.3</td>
<td>Prevalence and Correlates of Food Insecurity Among People Living with HIV</td>
<td>32</td>
</tr>
<tr>
<td>2.4.4</td>
<td>Impact of Food Insecurity on General Health Outcomes</td>
<td>34</td>
</tr>
<tr>
<td>2.4.5</td>
<td>Impact of Food Insecurity on HIV Transmission Risk</td>
<td>35</td>
</tr>
<tr>
<td>2.4.6</td>
<td>Impact of Food Insecurity on Access to HIV Treatment and Care Services</td>
<td>37</td>
</tr>
<tr>
<td>2.4.7</td>
<td>Impact of Food Insecurity on ART Outcomes</td>
<td>39</td>
</tr>
<tr>
<td>2.5</td>
<td>Discussion</td>
<td>43</td>
</tr>
</tbody>
</table>

### CHAPTER 3: PREVALENCE AND CORRELATES OF FOOD INSECURITY AMONG HIV-POSITIVE INDIVIDUALS RECEIVING ART ACROSS BC, CANADA

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>Synopsis</td>
<td>48</td>
</tr>
<tr>
<td>3.2</td>
<td>Introduction</td>
<td>49</td>
</tr>
<tr>
<td>3.3</td>
<td>Methods</td>
<td>50</td>
</tr>
<tr>
<td>3.3.1</td>
<td>Study Sample: LISA</td>
<td>50</td>
</tr>
<tr>
<td>3.3.2</td>
<td>Outcome Variable</td>
<td>50</td>
</tr>
<tr>
<td>3.3.3</td>
<td>Potential Explanatory Variables</td>
<td>51</td>
</tr>
<tr>
<td>3.3.4</td>
<td>Statistical Analyses</td>
<td>53</td>
</tr>
<tr>
<td>3.4</td>
<td>Results</td>
<td>53</td>
</tr>
<tr>
<td>3.5</td>
<td>Discussion</td>
<td>54</td>
</tr>
</tbody>
</table>
CHAPTER 4: RELATIONSHIP BETWEEN HUNGER, ADHERENCE AND PLASMA HIV RNA SUPPRESSION AMONG HIV-POSITIVE ILLICIT DRUG USERS RECEIVING ART IN METROPOLITAN VANCOUVER, BC ..................................................62

4.1 Synopsis ...........................................................................................................62
4.2 Introduction .......................................................................................................63
4.3 Methods ...........................................................................................................64
  4.3.1 Study Sample: ACCESS ...........................................................................64
  4.3.2 Variable Selection .....................................................................................64
  4.3.3 Statistical Analyses ..................................................................................66
4.4 Results ...............................................................................................................67
4.5 Discussion .........................................................................................................68

CHAPTER 5: RELATIONSHIP BETWEEN FOOD INSECURITY AND MORTALITY AMONG HIV-POSITIVE INJECTION USERS RECEIVING ART IN BC, CANADA ........78

5.1 Synopsis ...........................................................................................................78
5.2 Introduction .......................................................................................................79
5.3 Methods ...........................................................................................................80
  5.3.1 Study Sample: DTP ................................................................................80
  5.3.2 Variable Selection .....................................................................................81
  5.3.3 Statistical Analysis ..................................................................................83
5.4 Results ...............................................................................................................85
5.5 Discussion .........................................................................................................86

CHAPTER 6: SUMMARY DISCUSSION, RECOMMENDATIONS, FUTURE DIRECTIONS ..................................................................................................................97

6.1 Synopsis ...........................................................................................................97
6.2 Summary of Findings .......................................................................................97
6.3 Unique Contributions ......................................................................................100
6.4 Strengths and Limitations ..............................................................................102
  6.4.2 Measurement Tools ................................................................................102
  6.4.3 Sampling Methodology and Study Design ............................................103
  6.4.4 Analytic Techniques ...............................................................................104
6.5 Application of Research Findings .................................................................105
  6.5.1 Etiologic and Public Health Considerations ..........................................105
6.5.2 Intervention and Policy Recommendations ........................................... 107

6.6 Future Research Directions ........................................................................ 110
   6.6.1 Community-based Research ............................................................... 110
   6.6.2 Longitudinal Operations Research ......................................................... 111
   6.6.3 Meta-analyses ....................................................................................... 112

6.7 Conclusion ................................................................................................. 113

REFERENCES ................................................................................................... 115

APPENDIX 1: TREATMENT AS PREVENTION AND THE PUBLIC HEALTH
INTERVENTION TO ‘STOP HIV/AIDS’ IN BC .................................................. 139
   A-1.1 Treatment as Prevention ..................................................................... 139
   A-1.2 Public Health Intervention to ‘STOP HIV/AIDS’ in BC ...................... 141

APPENDIX 2: RADIMER/CORNELLSCALE: THE TOOL AND ITS VALIDATION .... 143
   A-2.1 Radimer/Cornell Scale ......................................................................... 143
   A-2.2 Validation of the Radimer/Cornell Scale ............................................... 145
      A-2.2.1 Construction on Well-grounded Theory ......................................... 145
      A-2.2.2 Construct Validity .......................................................................... 146
      A-2.2.3 Internal Consistency ...................................................................... 147
      A-2.2.4 Criterion-related Validity ............................................................... 147
      A-2.2.5 Accuracy ....................................................................................... 148
   A-2.3 Validation and Use in Specific Populations ......................................... 148
      A-2.3.1 Validation in North America ......................................................... 148
      A-2.3.2 Validation Cross-culturally ............................................................. 149

APPENDIX 3: REVISITING CONFOUNDER SELECTION: A DIRECTED ACYCLIC
GRAPH APPROACH ..................................................................................... 150
   A-3.1 Introduction .......................................................................................... 150
   A-3.2 Methods ............................................................................................... 151
      A-3.2.1 Directed Acyclic Graphs (DAGs) .................................................... 151
      A-3.2.2 DAG-theory Definition of Confounding ........................................ 152
A-3.2.3 Confounder Variable Selection ........................................... 153
A-3.3 Results.................................................................................. 154
A-3.4 Discussion ........................................................................... 154
LIST OF TABLES

Table 2.1 Prevalence of stunting and underweight among children under 5 years in sub-Saharan African countries with generalized HIV epidemics ...........................................46

Table 2.2 Prevalence of anemia and Vitamin A deficiency among women and children under 5 years in sub-Saharan African countries with generalized HIV epidemics ..........47

Table 3.1 Responses to Radimer/Cornell food security measures among HIV-infected individuals receiving highly active antiretroviral therapy in BC, Canada (n = 457) ........................................................................................................59

Table 3.2 Bivariate analysis of characteristics associated with food insecurity among HIV-infected individuals receiving highly active antiretroviral therapy in BC, Canada (n = 457) ........................................................................................................60

Table 3.3 Univariate and multivariate analyses of factors associated with food insecurity among HIV-infected individuals receiving highly active antiretroviral therapy in BC, Canada (n = 457) ........................................................................................................61

Table 4.1 Univariate analysis of factors associated with self-reported hunger among HIV-positive illicit drug users receiving antiretroviral therapy in Vancouver, BC (n = 375) ........................................................................................................74
Table 4.2 Univariate analysis of factors associated with plasma HIV RNA suppression among HIV-positive illicit drug users receiving antiretroviral therapy in Vancouver, BC (n = 406) ...........................................................................................................................................75

Table 4.3 Multivariate analysis of factors associated with plasma HIV RNA suppression among HIV-positive illicit drug users receiving antiretroviral therapy in Vancouver, BC (n = 406)...........................................................................................................................................76

Table 4.4 Multivariate analysis of factors associated with HIV RNA viral load suppression, stratified by adherence level, among HIV-positive illicit drug users receiving antiretroviral therapy in Vancouver, BC (n = 406)...........................................................................................................................................77

Table 5.1 Baseline characteristics among HIV-positive injection drug users initiating antiretroviral therapy across BC, by food security status, between June 1998 and Sept 2011 (n = 254) ...........................................................................................................................................92

Table 5.2 Baseline characteristics among HIV-positive injection drug users initiating antiretroviral therapy across BC, by all-cause mortality status, between June 1998 and Sept 2011 (n = 254)...........................................................................................................................................93

Table 5.3 Unadjusted and adjusted factors associated with all-cause mortality among HIV-positive injection drug users initiating highly active antiretroviral therapy in BC, between June 1998 and Sept 2011 (n = 254)...........................................................................................................................................94
Table A-2.1 Radimer/Cornell Scale: Household and Individual Level........................................144

Table A-3.1 Multivariate analysis of factors associated with HIV RNA viral load suppression among HIV-positive illicit drug users receiving antiretroviral therapy in Metropolitan Vancouver, BC (n = 406) ..........................................................................................................................158
LIST OF FIGURES

Figure 1.1 Adapted risk environment framework: Schematic of the relationship between food insecurity and HIV outcomes among positive illicit drug users in Vancouver, BC ..... 13

Figure 5.1a Crude cumulative incidence of all-cause mortality among HIV-positive injection drug users initiating antiretroviral therapy, stratified by food security status .............. 95

Figure 5.1b Crude cumulative incidence of all-cause mortality among HIV-positive injection drug users initiating antiretroviral therapy, stratified by hunger status ............... 95

Figure 5.2a Crude cumulative incidence of all-cause mortality among HIV-positive injection drug users initiating antiretroviral therapy, stratified by food security and body mass index levels ........................................................................................................................................ 96

Figure 5.2b Crude cumulative incidence of all-cause mortality among HIV-positive injection drug users initiating antiretroviral therapy, stratified by hunger and body mass index levels ........................................................................................................................................ 96

Figure A-3.1 Hypothesized relationships between variables considered in the relationship between hunger and plasma HIV RNA suppression among HIV-positive illicit drug users receiving antiretroviral therapy in Metropolitan Vancouver, BC .................. 157
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCESS</td>
<td>AIDS Care Cohort to Evaluate access to Survival Services</td>
</tr>
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<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
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<tr>
<td>AMPATH</td>
<td>Academic Model Providing Access to Healthcare</td>
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<td>AOR</td>
<td>Adjusted Odds Ratio</td>
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<td>ART</td>
<td>Antiretroviral therapy</td>
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<td>ARV</td>
<td>Antiretroviral (medication)</td>
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<td>BC</td>
<td>British Columbia</td>
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<td>BC-CfE</td>
<td>British Columbia Centre For Excellence in HIV/AIDS</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>CD4</td>
<td>Cluster of Differentiation</td>
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<td>CES-D 10</td>
<td>Center for Epidemiological Studies Depression scale</td>
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<td>China CDC</td>
<td>Chinese Centre for Disease Control and Prevention</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>DAG</td>
<td>Directed Acyclic Graph</td>
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<td>DTES</td>
<td>Downtown Eastside</td>
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<tr>
<td>DTP</td>
<td>Drug Treatment Program</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>EURO-NONOPEP</td>
<td>European Project on Non-Occupational Post-Exposure Prophylaxis for HIV</td>
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<tr>
<td>FAO</td>
<td>Food and Agriculture Organization of the United Nations</td>
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<tr>
<td>FANTA-2</td>
<td>Food and Nutritional Technical Assistance (Project)</td>
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<td>HCV</td>
<td>Hepatitis C Virus</td>
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<td>HFIAS</td>
<td>Household Food Insecurity Access Scale</td>
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<td>HHS</td>
<td>Household Hunger Scale</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>IAS</td>
<td>International AIDS Society</td>
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<td>Injection Drug Users</td>
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<td>IQR</td>
<td>Inter-quartile Range</td>
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<td>IFPRI</td>
<td>International Food and Policy Research Institute</td>
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<td>LISA</td>
<td>Longitudinal Investigation into Supportive and Ancillary health services</td>
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<td>MPR</td>
<td>Medication Possession Ratio</td>
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<td>MTCT</td>
<td>Mother-To-Child-Transmission</td>
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<td>NRTI</td>
<td>Nucleoside Reverse Transcriptase Inhibitor</td>
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<td>NNRTI</td>
<td>Non-Nucleoside Reverse Transcriptase Inhibitor</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>PEPFAR</td>
<td>President’s Emergency Program for AIDS Relief</td>
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<td>PI</td>
<td>Protease Inhibitor</td>
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<tr>
<td>RCT</td>
<td>Randomized Control Trial</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
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<tr>
<td>STOP HIV/AIDS</td>
<td>Seek and Treat for Optimal Prevention of HIV/AIDS</td>
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<tr>
<td>STROBE</td>
<td>Strengthening the Reporting of Observational Studies in Epidemiology</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<td>UNAIDS</td>
<td>Joint United Nations Programme on HIV/AIDS</td>
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<tr>
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<td>US-HFSSM</td>
<td>United States Household Food Security Survey Module</td>
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<td>USA</td>
<td>United States of America</td>
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<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>Acronym</td>
<td>Full Form</td>
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<td>VIF</td>
<td>Variance Inflation Factor</td>
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<td>World Food Programme</td>
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<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
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CHAPTER 1: BACKGROUND, RATIONALE, OBJECTIVES

1.1 Synopsis

Chapter 1 will introduce readers to the definition of food insecurity and global prevalence estimates of its three components - food insufficiency, diversity and safety. It will describe the global burden and impacts of HIV/AIDS (Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome), and review recent progress and innovations in HIV treatment. The Chapter describes the geographic overlap and causal inter-relationship between food insecurity and HIV/AIDS at the individual, household and populations levels. It reviews food security- and nutrition-related risk factors and outcomes among HIV-positive illicit drug users, who represent a vulnerable and under-studied group. This Chapter presents a novel risk environment concept that will be used to frame study objectives, analyses and findings regarding the relationship between food insecurity and HIV outcomes among illicit drug users. It outlines critical gaps in knowledge regarding the prevalence and impacts of food insecurity on HIV treatment in the general HIV-positive population, as well as among HIV-positive illicit drug users, in British Columbia (BC), Canada. The Chapter prepares the reader for subsequent Chapters by articulating the proposed study objectives, hypotheses, setting and design.

1.2 Global Overview of Food Insecurity and HIV

The right to food is considered a basic human right and is fundamental to global public health (1, 2). An essential precursor to this right is food security, which the United Nations defies as a state where “all people, at all times, have physical, social and
economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life” (3). The number of people who are food insecure globally remains unknown. However, prevalence estimates based on surrogate markers such as undernutrition, micronutrient deficiencies and food-borne illnesses suggest that several billion people may be food insecure worldwide. Over 1 billion people are estimated to suffer from insufficient consumption of food (4), including approximately 115 million underweight and 178 million stunted children under five years (5). Poor dietary diversity in many parts of the world has resulted in over 2 billion people living with deficiencies of iodine, vitamin A or iron (6), and has contributed to a growing obesity epidemic in both high and low resource settings (7-9). The World Health Organization (WHO) estimates that 2.2 million people die per year from food and water-borne diarrheal diseases (10). Food insecurity has an unprecedented impact on global health outcomes. Insufficient consumption of food alone is estimated to be a top health risk worldwide, killing more people annually than HIV/AIDS, malaria and tuberculosis combined (11), and its reduction is a global priority as stipulated by the Millennium Development Goals (Target 1.C).

Existing in parallel to the global food security crisis is the HIV/AIDS pandemic. At the end of 2010, there were an estimated 33.3 million people living with HIV, including 2.6 million new infections, and 1.8 million AIDS-related deaths (12). The advent of triple combination highly active antiretroviral therapy (ART) has changed the trajectory of the epidemic, reducing HIV-related morbidity and mortality (13-15), lowering risk of transmission between sero-discordant contacts (16-18), and decreasing incidence of HIV at the population level (19-21). Global access to ART is expanding rapidly. An estimated 6.6 million people were receiving ART in low and middle-resource countries in 2010, representing an increase of 1.35 million from the year before and 47% of individuals deemed clinically eligible for treatment, according to recent WHO guidelines
Dramatic improvements in ART uptake globally over the past ten years and recognition of its public health impacts have led the Joint United Nations Programme on HIV/AIDS (UNAIDS) to ambitiously launch a global effort to “get to zero” – that is to achieve “zero new HIV infections, zero AIDS-related deaths and zero HIV-related discrimination” by the year 2015 (12).

1.3 Inter-relationship Between Food Insecurity and HIV/AIDS

Food insecurity and HIV have been described as “syndemic”, meaning epidemics that coexist and perpetuate each other (22). The geographic overlap in prevalence of food insecurity and HIV/AIDS is most pronounced in sub-Saharan Africa, which has both the highest proportion of people who are undernourished and HIV-positive in the world (3, 12). The dual epidemics are also evident in Asia, which has the highest number of undernourished people in the world and which has seen exponential increases in new HIV infections over the past 10 years (3, 12). Similarly, elevated rates of food insecurity and HIV have been shown to exist in high resource settings among specific populations. The demographic overlap between these health crises has left certain groups particularly vulnerable, notably children and women, as well as people suffering from mental health disorders, homelessness and addiction (23, 24).

Indeed the co-occurrence of food insecurity and HIV/AIDS is not coincidental, as each condition has been shown to adversely impact the other. The relationship between food insecurity and HIV/AIDS is frequently referred to as a “vicious cycle”, because each condition worsens the risk for, and outcomes of, the other at the individual, household and population level (23-26). HIV/AIDS affects an individual’s nutritional status by increasing metabolic rate and nutrient requirements, while simultaneously impeding nutrient absorption, utilization, and socio-economic access to food. HIV/AIDS contributes
to household food insecurity by increasing caregiver burden, which in turn reduces household economic productivity and purchasing power. HIV-related morbidity and mortality is believed to contribute to population-level reductions in agricultural production and economic development (25). It is therefore unsurprising that a high proportion of people living with HIV/AIDS has been found to be food insecure in both high and low resource settings (23, 24). Conversely, food insecurity is believed to lead to adverse HIV clinical outcomes through diverse behavioural, nutritional and mental health pathways (24), and has been associated with increased risk of transmission, late access to treatment and care, non-adherence to ART, poor immunologic and virologic ART response, and increased risk of mortality (23-26).

1.4 Food Insecurity Among HIV-Positive Illicit Drug Users

There were between 155 and 250 million illicit drug users worldwide in 2009 (27), including an estimated 16 million injection drug users (IDU) (28). Illicit drug users face multiple structural and social barriers to accessing health care and social support services, which collectively serve to compound health risks and exacerbate poor health outcomes (29). Illicit drug users are vulnerable to developing malnutrition, and often simultaneously experience numerous forms of macro- and micro-nutrient deficiencies (30, 31). Caloric insufficiency among illicit drug users has been associated with an array of harms, including decreased immune function (32), elevated risk of a positive tuberculin test (33), invasive candidiasis, viral hepatitis, bacterial pneumonia, and subcutaneous and perianal abscesses (31). Illicit drug users living with HIV may have increased risk of developing food insecurity and nutritional deficiencies when compared to uninfected individuals, due to reduced socio-economic access to food, inadequate food consumption patterns, and adverse HIV- and drug-nutrient metabolic alterations.
(32, 34-36). Some studies have found that food insecurity and malnutrition among HIV-positive drug users are associated with increased transmission risk behaviors (37), HIV-related wasting (35) and mortality (34). However, evidence regarding the relationship between food insecurity and adverse ART outcomes among illicit drug users is limited (38-40).

1.5 Conceptual Frameworks

In public health and epidemiology, conceptual frameworks have been used to describe the complex inter-relationships between determinants of health, and hierarchies in their biological and social constructs (41). This dissertation utilizes a novel risk environment framework to understand individual and environmental food security-related risks and harms experienced by HIV-positive illicit drug users. Building on an original concept developed by Rhodes et al. (42, 43), this adapted framework incorporates and inter-links three pre-existing frameworks specific to food security and HIV/AIDS: i) theoretical ‘dimensions’ of food security defined by the United Nations World Food Programme (WFP); ii) theorized causal pathways connecting food insecurity and adverse HIV outcomes, developed by Weiser et al; and iii) the clinical and public health concept of HIV treatment as prevention promulgated by Montaner et al.

The following section will briefly review the original risk environment framework developed by Rhodes and colleagues, and outline additional theoretical and etiologic frameworks developed by the WFP, Weiser and Montaner. This section will then present a schematic and explanation for the new, adapted risk environment framework which has integrated the former concepts, and which will be used to guide study design, analysis and interpretation in this dissertation.
1.5.1 Rhodes’ Risk Environment Framework

Over the past two decades, there has been a growing recognition among researchers and public health bodies that poor health outcomes among illicit drug users are not only produced and perpetuated by individual-level factors, such as socio-demographic status, behaviors and clinical status; but, are also shaped by drug users’ environment. Rhodes et al. conceived a heuristic, the risk environment framework, which calls for a shift away from a focus on individual-level drivers of drug-related harm, to an understanding that drug-related harms are generated and perpetuated by physical, social, economic and policy environments (43). Under this conceptualization, the risk environment of drug users is seen as a “product of interplay” between different types of and levels (micro, meso and macro) of environmental factors, which are “locally produced” and inherently context-specific (42). Micro-level environmental factors shaping the risk environment of drug users may include neighborhood disadvantage and transition; physical injection environment; prisons structures; social norms, networks and capital; and law enforcement. Meanwhile, at the meso and macro-levels, the risk environment may be influenced by factors such as public, legal, criminal justice, economic, gender and cultural structures and systems (42, 43). These types and levels of environmental risk are seen to be inextricably connected, and to interact with individual-level risk factors in order to heighten drug users’ vulnerability to diverse harms and adverse health outcomes. Rhodes’ risk environment framework has been widely adopted as a heuristic by researchers to understand the complex inter-relationship between individual and environmental-level factors influencing drug-related risks and outcomes. From a public health perspective, this heuristic suggests that reducing the risk environment of drug users, rather than focusing solely on individual-level risks, can effectively attenuate drug-related harms and HIV risks (42).
In the current dissertation, Rhodes’ original risk environment framework will be used as a platform from which to build an adapted, locally-appropriate risk environment framework that considers the individual and environmental factors shaping food insecurity, adverse HIV outcomes and other harms specific to illicit drug users in the context of BC.

1.5.2 World Food Program’s Dimensions of Food Security

The growing body of literature linking food insecurity and malnutrition to poor health outcomes among illicit drug users highlights the importance of considering food insecurity as an individual and environmental risk factor within the risk environment framework. Multilateral agencies involved in global food / nutrition programs and policies have developed an operational concept of food security that is amenable to integration into Rhodes’ original risk environment framework.

The WFP and FAO have promulgated a theoretical framework that views food security as constituting three broad and intersecting ‘dimensions’: individual-level food utilization, household-level food access and population-level food availability (25, 44). Under this framework, food utilization is viewed as constituting: i) individual-level food consumption patterns (i.e. amount, quality and safety of foods consumed), which is influenced by social and behavioral factors; and ii) biological use of food (i.e. metabolization of nutrients), which is determined by physiological functions (45). Food access is conceptualized as occurring at the household level, and affected by factors such as purchasing power, social and physical access. Food availability is viewed as a population-level dimension, influenced by factors such as climate, seasonality, political security and economic trade. This conceptual framework includes an overarching dimension of food stability (46) to emphasize that food security can only exist when
these dimensions of food utilization, access and availability are sustainable. Food insecurity is seen to affect individuals, households and populations on a permanent (chronic) or temporary (transitory) basis, or in cycles (46). Implicit in this notion is that food insecurity at the individual-level is influenced by household- and population-level dimensions of food insecurity.

The adapted risk environment framework proposed in this dissertation integrates all four WFP-defined dimensions of food insecurity (see Section 1.5.5). Empirical studies in this dissertation will focus on the individual-level (specifically the food consumption aspect of food utilization) and household-level (i.e. food access) experiences of food insecurity among illicit drug users.

1.5.3 Weiser’s Bi-directional Pathways Between Food Insecurity and HIV Outcomes

Rhodes’ original risk environment framework suggests that individual and environmental risk factors produce harms and HIV risks through diverse biological and social mechanisms. In order to understand the possible relationship between food insecurity and HIV outcomes among illicit drug users, Rhodes’ risk environment framework can be enhanced to consider specific etiologic pathways hypothesized to link food insecurity and HIV outcomes.

Weiser et al. (2012) recently published a conceptual framework that describes food insecurity and HIV/AIDS as bi-directionally linked through distinct nutritional, mental health and behavioural pathways (24). In terms of nutritional pathways, severe food insufficiency and poor dietary diversity can increase risk of HIV-related morbidity and mortality via pathways of undernutrition (e.g. low body mass index) and micronutrient deficiencies. Regarding mental health mechanisms, food insecurity has been linked to
symptoms of depression, illicit drug use and problem alcohol use, which have been individually associated with reduced ART adherence, and worse immunologic and virologic status. Finally food insecurity is understood to lead to HIV disease progression through behavioural mechanisms, by contributing to ART non-adherence, missed clinical visits and treatment interruptions.

The adapted risk environment framework proposed in this dissertation integrates Weiser et al.’s theorized etiologic framework to explain potential linkages between food insecurity and adverse HIV outcomes among drug users (see Section 1.5.5). Empirical studies in this dissertation will draw on Weiser’s conceptual framework to guide study objectives and analyses seeking to explore potential links between individual-level food insecurity (i.e. food utilization) and poor clinical outcomes HIV-positive illicit drug users, within an adapted risk environment framework.

1.5.4 Montaner’s HIV Treatment as Prevention

Rhodes’ risk environment framework considers how individual and environmental factors shape illicit drug users’ risk of HIV transmission, and can be modified to additionally consider the impact of these risks on other clinical and population-level HIV outcomes. In the era of highly active ART, public health heuristics used to understand drug-related HIV risk require consideration of a recent scientific breakthrough: HIV treatment as prevention.

Montaner et al. (2006) promulgated a hypothesis that ART uptake and adherent use by all people living with HIV/AIDS could eliminate HIV transmission between sero-discordant contacts, and curb HIV incidence at the population level (47). This hypothesis was based on extensive empiric evidence from studies examining the impact of ART use in the context of mother-to-child transmission (MTCT), sexual and needle-stick pre- and
post-exposure, and longitudinal and ecologic studies (48, 49), and was further supported by mathematical modeling (50, 51). In 2011, a major scientific breakthrough proved the preventive role of ART by means of a randomized control trial (RCT). This study involving 1,763 sero-discordant couples found that early initiation of ART was associated with a 96% reduction in HIV transmission (16). The rapid expansion of ART access has been globally adopted by public health officials on cost-effectiveness and human rights bases (52). In BC, the *HIV treatment as prevention* concept led to the initiation of a novel pilot intervention to Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS) (53). Appendix 1 briefly reviews scientific evidence informing *HIV treatment as prevention*, and outlines related public health initiatives in BC and internationally.

The adapted risk environment framework proposed in this dissertation draws on *HIV treatment as prevention* to interpret the effect of individual outcomes on population outcomes (see Section 1.5.5). Empirical analyses will draw on the *HIV treatment as prevention* concept to ground study objectives and interpretations within a public health lens that sees ART as a potent synergistic strategy for reducing individual and population-level HIV morbidity, mortality and transmission.

### 1.5.5 Adapted Risk Environment Framework

This dissertation draws on a novel risk environment framework to delineate the multiple individual and (socio-structural, physical and policy) environmental factors theorized to produce food security-related harms and adverse HIV outcomes among illicit drug users in BC. Depicted in Figure 1.1, this schematic views food insecurity and associated adverse HIV outcomes as the product of complex and dynamic interactions between individuals and their micro-, meso- and macro-environments. Building on Rhodes’ original framework and drawing on the WFP ‘dimension’ of food insecurity, this
adapted framework views individual socio-demographic, behavioral and clinical factors (including food utilization) as interacting with socio-structural, physical and policy environments (including household-level food access, population-level food availability and municipal/provincial food-based policies) to create and exacerbate specific drug-related harms among individual drug users. Food insecurity at the individual and environmental levels is theorized to lead to specific types of harms among HIV-positive illicit drug users, notably micro/macronutrient malnutrition, mental health disorders and poor HIV disease management behaviors. Drawing on Weiser’s etiologic framework, these harms or intermediate health outcomes are seen to act as pathways towards a range of adverse HIV outcomes, including biological transmission risk, opportunistic infection, reduced pharmacokinetic efficacy, poor immunologic and virologic response to ART and reduced survival. From a public health perspective, these poor HIV outcomes at the individual level translate to adverse epidemiologic trends at the population level, and notably to increased HIV incidence and AIDS-related mortality.

This adapted risk environment framework provides a heuristic from which to contextualize study objectives, design, analytic techniques and interpretation of results. Study objectives in this dissertation will focus on evaluating risk factors associated with food insecurity (i.e. food utilization) and associated HIV outcomes at the individual level. Applying different study designs and analytic techniques, it will explore the potential causal linkages between food utilization and HIV outcomes through nutritional, mental health or behavioral pathways. The public health relevance of study findings will be interpreted in light of the HIV treatment as prevention conceptual framework, which emphasizes individual-level optimization of ART use as the cornerstone of effective public health approaches to reducing the population-level HIV-related morbidity, mortality and transmission. Additionally, results will be interpreted within a risk environment public health framework that recognizes the value of altering the risk
environment of drug users to “enable” adoption of risk reduction strategies at the individual-level.
Figure 1.1: Adapted Risk Environment Framework: Schematic of the relationship between food insecurity and HIV outcomes among HIV-positive illicit drug users in Vancouver, BC

HIV-positive illicit drug users

Factors at individual level
- Individual-level food utilization (intake and absorption) of sufficient, diverse and safe foods
- Gender
- Age
- Ethnicity
- Education
- Income
- Housing, neighborhood
- History of incarceration
- Mental health status
- Type and intensity of illicit drug use

Socio-structural factors in Micro-environment
- Household-level physical, social & economic access to sufficient, diverse and safe foods
- Social, cultural and economic factors shaping access to:
  - HIV treatment and care services
  - Harm reduction and drug treatment services
  - Mental health services
  - Affordable, safe and respectable housing
  - Social support and employment services

Physical factors in Meso-environment
- Population-level physical availability of sufficient, diverse and safe foods
- Factors shaping physical availability and proximity to:
  - HIV treatment and care services
  - Harm reduction and drug treatment services
  - Mental health services
  - Affordable, safe and respectable housing
  - Social support and employment services

Policy factors in Macro-environment
- Stability of provincial/municipal policies that sustain utilization, access and availability of sufficient, diverse and safe foods
- Factors shaping stability of political and legislative policies supporting access and availability of:
  - Universal healthcare and free ART
  - Low threshold harm reduction and drug treatment services
  - Mental health services
  - Affordable, safe and respectable housing
  - Social support and employment services

Factors at the individual level interact with socio-structural, physical, and policy environmental factors at micro, meso, and macro levels to produce food insecurity (i.e., poor food utilization) and drug-related harms.

Weizer Conceptual Framework: theorized causal pathways between food insecurity and HIV outcomes—nutritional, mental health and behavioral

Weizer Conceptual Framework: theorized causal pathways between food insecurity and HIV outcomes—nutritional, mental health and behavioral

Montaner Conceptual Framework: HIV Treatment as Prevention

Primary HIV outcomes at individual level
- Risk of biological HIV transmission
- Pharmacokinetic antiretroviral efficacy
- Opportunistic infections
- CD4 cell count
- Viral load
- Mortality

Intermediate nutrition health outcomes at individual level
- Micronutrient malnutrition
- Macronutrient malnutrition

Intermediate mental health outcomes at individual level
- Depression
- Anxiety

Intermediate behavioral outcomes at individual level
- HIV transmission risk behavior
- Hospital utilization
- ART access and uptake
- Adherence / loss-to-follow up

Intermediate behavioral outcomes at individual level
- HIV transmission risk behavior
- Hospital utilization
- ART access and uptake
- Adherence / loss-to-follow up

Among HIV-positive illicit drug users, food insecurity leads to adverse intermediate nutritional, mental health and behavioral outcomes, which in turn act as pathways leading to adverse HIV clinical outcomes.

Primary HIV outcomes at individual level
- Risk of biological HIV transmission
- Pharmacokinetic antiretroviral efficacy
- Opportunistic infections
- CD4 cell count
- Viral load
- Mortality

Secondary HIV outcomes at population level
- Incidence
- Mortality

Poor HIV clinical outcomes at the individual level translate to adverse secondary outcomes at the population level. From a public health perspective, optimization of individual clinical outcomes is essential to reduce morbidity, mortality and transmission at the population level.
1.6 Global and Local Gaps in Knowledge

Understanding the international evidence regarding the relationship between food insecurity and HIV treatment outcomes is essential to guiding empirical studies. Previous review articles have summarized the links between food insecurity and HIV outcomes (26, 54, 55), but have not specifically examined the potential impacts of food utilization and access in the era of ART. **Critical gaps in understanding remain regarding the relationships between food insecurity and HIV transmission, access to treatment and care, adherence to ART, pharmacokinetic effectiveness of antiretrovirals, immunologic and virologic responses to ART, and survival.**

In the context of BC, specific gaps in knowledge persist regarding the current prevalence, risk factors and clinical effects of food insecurity among HIV-positive individuals receiving ART. Ten years ago a province-wide study found that 48% of individuals newly initiating HIV treatment were food insecure, and 21% experienced hunger (56). Since then the province, and particularly Metropolitan Vancouver, have experienced ongoing socio-demographic and economic shifts that have worsened the risk environments of some vulnerable groups. Although BC currently has the largest number of millionaires per capita, it also has the highest proportion of people living below the poverty line of all provinces in Canada (57). Once known as the world’s ‘most livable city’, Metropolitan Vancouver is now infamous for its income inequities and marginalization of the urban poor (58). Lack of affordable housing, extensive wait lists for social housing and insufficient supply of supportive housing have increased homelessness in Metropolitan Vancouver (59). Gentrification and police crackdowns in the city’s Downtown Eastside (DTES) have displaced illicit drug users and other HIV-vulnerable groups to peripheral areas, reducing their access to vital medical and harm reduction services (60). Taken together, these
changes suggest that people living with HIV/AIDS in BC, and specific hard-to-reach individuals, may be more vulnerable to food insecurity than 10 years ago, and highlight a need to re-evaluate the prevalence and correlates of food insecurity among HIV-positive individuals receiving ART in the province.

Illicit drug use has been previously identified as a key risk factor for hunger among individuals receiving ART in BC (56). Findings from a recent study among 1,053 HIV-negative illicit drug users in Metropolitan Vancouver found that 65% reported being ‘hungry and unable to afford enough food’ (56), and suggests that the current prevalence of hunger among HIV-positive illicit drug users may be equal or higher. While studies have identified a broad range of social and structural barriers to effective ART use among illicit drug users (61-63), the roles of food insecurity and hunger have received little attention. Evidence suggests that hunger may lead to adverse HIV outcomes through diverse nutritional, mental health and behavioural pathways (24), but research informing these mechanisms has been largely conducted in non-illicit drug user populations. Among the few studies that have assessed the relationship between hunger and disease progression among HIV-positive illicit drug users, results have been inconsistent and limited by small sample sizes (38, 64). Food insecurity has been associated with increased risk of mortality among individuals receiving ART (65). No studies have evaluated the long-term consequences of food insecurity and hunger on survival among illicit drug users. As efforts are currently underway to expand HIV testing and treatment to all clinically eligible individuals in BC, there is an imperative to ensure that IDU benefit equally and optimally from ART use (66, 67). To this end, there is an urgent need to explore whether hunger is a barrier to effective ART use among illicit drug users in this setting.
1.7 Study Objectives and Hypotheses

In light of the gaps in knowledge and research needs described above, the overall aim of this dissertation is to identify the current prevalence and risk factors of food insecurity among HIV-positive individuals, and specifically the effects of hunger on HIV clinical outcomes among illicit drug users receiving ART in BC. Study objectives and hypotheses for this dissertation are:

1. **To review published evidence regarding the impact of food insecurity on HIV treatment outcomes.** Current knowledge regarding the relationship between food insecurity (specifically, the ‘dimension’ of food utilization) and HIV-related outcomes in the ART era is limited. Amalgamation and critical review of this literature is essential to contextualize the proposed empirical research among people living with HIV in BC.

2. **To assess the prevalence and correlates of general food insecurity among hard-to-reach HIV-positive individuals receiving ART in BC.** In light of the elevated prevalence of food insecurity and hunger among individuals receiving ART in BC 10 years ago (56), and subsequent changes in the risk environment of people living with HIV in BC, and particularly in the DTES of Metropolitan Vancouver, this study assumes the following hypothesis:

   *Hypothesis 1:* The prevalence of food insecurity and hunger among hard-to-reach individuals receiving ART in BC will be higher than 48% and 21%, respectively, as reported 10 years ago (56). Food insecurity will be
independently associated with female gender, Aboriginal ancestry, having an income below current poverty-level thresholds, unstable housing, living in the DTES of Vancouver, IDU status and adverse health outcomes.

3. **To explore the relationship between hunger and plasma HIV RNA suppression among IDU receiving ART in Metropolitan Vancouver.** Considering current levels of hunger among HIV-negative illicit drug users in this setting (68), evidence regarding the heightened vulnerability of HIV-positive people to food insufficiency (26, 54, 55), and studies suggesting an inverse association between food insecurity/hunger and plasma HIV RNA suppression (64, 69), this study assumes the following hypothesis:

_{Hypothesis 2:} The prevalence of hunger among HIV-positive illicit drug users receiving ART in Metropolitan Vancouver will be higher than 65% (68), and will be independently associated with reduced likelihood of achieving plasma HIV RNA suppression.

4. **To examine the impact of food insecurity and hunger on mortality among illicit drug users receiving ART across BC.** No studies have evaluated the effect of food insecurity or hunger on survival among IDU receiving ART. The only existing study was conducted in the general HIV population in BC, and found that food insecurity was associated with an increased risk of mortality, particularly among undernourished individuals (65). This study therefore assumes the following hypothesis:
Hypothesis 3: Food insecurity and hunger are independently associated with increased risk of mortality among IDU receiving ART, and the magnitude of this relationship will be greatest among IDU with low body mass index.

1.8 Study Setting, Design and Methods

The proposed hypothesis-driven studies are presented in Chapters 3, 4 and 5, respectively. These quantitative studies draw on clinical and laboratory data from socio-demographic and behavioural surveys from observational studies. Ethics approval for the overall study proposed was obtained from the Providence Health Care / University of British Columbia Research Ethics Board (H12-03050). To prevent duplication, these studies are described here in detail and summarized briefly in forthcoming Chapters.

1.8.1 Longitudinal Investigation into Supportive and Ancillary health services (LISA)

Study objective 2 of this dissertation (i.e. to assess the prevalence and correlates of general food insecurity among HIV-positive individuals receiving ART in BC) will be evaluated within the LISA cohort. This is a closed observational study of individuals exposed to triple combination ART across BC. The LISA cohort has been described in detail elsewhere (70). Eligibility for the LISA cohort included: being 19 years of age or older at enrollment, residing in BC, and previously accessing ART. Participants were recruited between July 2007 and January 2010 via ARV-prescribing physicians and community-sites providing medical and social support services. The LISA study was designed to over-represent hard-to-reach populations. A 45-minute interviewer-administered survey elicited information about participant socio-demographic
characteristics, sexual and drug use behaviours, and self-reported clinical factors. Participants provided voluntary written informed consent to link survey response data to clinical and laboratory data contained in the HIV/AIDS DTP database. Ethical approval for the LISA study was obtained from the Research Ethics Boards of University of British Columbia/Providence Health Care (H06-00265).

1.8.2 AIDS Care Cohort to Evaluate access to Survival Services (ACCESS)

Study objective 3 of this dissertation (i.e. to explore the relationship between hunger and plasma HIV RNA suppression among IDU receiving ART in Vancouver) will be evaluated within the ACCESS cohort. Initiated in 1996, ACCESS is an open prospective cohort of HIV-positive illicit drug users in the Metropolitan area of Vancouver. The ACCESS cohort has been described in detail elsewhere (71, 72). In brief, participants are recruited using snowball sampling and street-based outreach, focused in the DTES of Vancouver, using word-of-mouth, postering and other methods at harm reduction services, single room occupancy hotels, drug-use areas and healthcare settings. Individuals are eligible for inclusion if they are aged 18 years or older; are HIV-seropositive; and have used illicit drugs other than cannabinoids in the month prior to enrollment. Every six months from baseline, ACCESS participants undergo a nurse examination, provide blood samples, and complete an interview-administered questionnaire about their socio-demographic status, HIV risk behaviours, drug-use patterns and healthcare utilization. Participants receive an honorarium of CAD$20 each study visit. Linkage of survey responses with DTP data is facilitated by participant written informed consent. Ethics approval for ACCESS is obtained annually from the Providence Health Care/University of British Columbia Research Ethics Board (H05-50233).
1.8.3 HIV/AIDS Drug Treatment Program (DTP)

Study objective 4 of this dissertation (i.e. to examine the impact of food insecurity and hunger on mortality among illicit drug users receiving ART across BC) will be evaluated within the DTP cohort. In BC, ARVs have been distributed free of charge to HIV-infected individuals since 1986, and coordinated centrally since 1992 by the BC-CfE’s HIV/AIDS DTP, located at St. Paul’s Hospital. Details of the HIV/AIDS DTP have been described elsewhere (13). In brief, clinical eligibility for receipt of ART in BC is based on guidelines generated by the BC-CfE Therapeutic Guidelines Committee, and are consistent with current recommendations by the International AIDS Society – USA (73). When people initiate HIV therapy in BC, triple combination ART consists of two nucleosides (NRTI), or an NRTI and a nucleotide reverse transcriptase inhibitor as a backbone, plus either i) a non-boosted protease inhibitor (non-boosted PI), ii) a non-nucleoside reverse transcriptase inhibitor (NNRTI), or iii) a protease inhibitor boosted with ritonavir (boosted PI) (74).

Physicians of HIV-infected individuals must complete a drug request form, which acts as a legal prescription, to enroll an eligible individual on ART. HIV/AIDS DTP enrollment forms elicit information about patient socio-demographic status, HIV-specific drug history, CD4 cell counts, plasma HIV RNA levels, current drug prescription, and the enrolling physician. Prospective clinical, virologic, immunologic and drug-regimen data is collected on a quarterly basis. Epidemiological studies performed on DTP data form the basis of ongoing revisions to the BC-CfE’s province-wide HIV treatment guidelines (74). Patients provide voluntary written informed consent for the BC-CfE to access electronic medical records for research purposes. Ethical approval for government-mandated analyses is obtained on an annual basis from the Providence Health Care / University of British Columbia Research Ethics Board (H05-50123).
1.9 Summary

This PhD dissertation is structured into six Chapters. Chapter 1 describes the background, rational and objectives of the study. It provides an overview of global prevalence of and relationships between food insecurity and HIV in the ART era; a review of relevant conceptual frameworks, the study rationale and objectives; and describes the study setting and design. Chapter 2 reviews current evidence and gaps in knowledge regarding the relationship between food insecurity and HIV clinical outcomes. Drawing on studies in both high and low resource settings, the literature review explores the potential impact of food insecurity on HIV transmission, access to HIV treatment and care, adherence to ART, pharmacokinetic effectiveness of ART, immunologic and virologic outcomes, and on survival. Chapter 3 draws on data from the LISA cohort to examine the prevalence and correlates of food insecurity and hunger among hard-to-reach individuals receiving ART across BC. Chapter 4 explores the association between hunger and plasma HIV RNA suppression among illicit drug users receiving ART in the Vancouver-based ACCESS cohort. Chapter 5 longitudinally examines the relationship between food insecurity/hunger and time to death among IDU receiving ART in the BC-wide HIV/AIDS DTP. Chapter 6 describes the study significance and contribution to global understandings of the relationship between food security, hunger and HIV treatment outcomes. It describes unique contributions and the strengths and limitations of the study design, measurement tools and analytic methods. Finally, it suggests avenues for the potential application of research findings to public health policies and future research.
CHAPTER 2: IMPACT OF FOOD INSECURITY ON HIV OUTCOMES: A REVIEW OF CURRENT KNOWLEDGE, GAPS AND RESEARCH PRIORITIES

2.1 Synopsis

**Background:** Literature regarding the potential impacts of food insecurity on HIV outcomes is limited. None has considered the diverse definitions and measures of food insecurity or its impacts on HIV in the ART era. **Methods:** The objectives of Chapter 2 are to review current definitions, measures and prevalence estimates of food insecurity, and to summarize evidence from high and low resource settings regarding its impacts on HIV outcomes in the era of ART. The Chapter applies a *scoping review approach* to consider a broad range of qualitative and epidemiological literature, and to categorize evidence thematically. **Results:** Food insecurity constitutes food insufficiency (hunger), poor dietary diversity and poor food safety. Validated epidemiological scales exist to measure food insecurity; academic and programmatic stakeholders additionally use a range of qualitative self-reported measures and objective nutritional markers to measure food insecurity. Risk factors of food insecurity vary between high and low resource settings. Evidence suggests that food insecurity is associated with horizontal and vertical risk of HIV transmission, reduced access and poor adherence to HIV treatment and care, pharmacokinetics of ARVs, immunological and virological outcomes, and reduced survival. Gaps in understanding persist regarding the causal mechanisms linking food insecurity to these adverse outcomes, and highlight a need for further research using robust study designs. **Discussion:** Operational research should be integrated into programmatic responses to these overlapping epidemics in order to identify effective and context-specific food security interventions for people living with HIV/AIDS.
2.2 Introduction

Food insecurity and HIV/AIDS are intertwined in a vicious cycle that heightens vulnerability to, and worsens the severity of, each condition at the individual, household and population levels (26, 75, 76). A growing body of evidence suggests that food insecurity may affect behavioural risk of HIV transmission (37, 77), reduce access to HIV treatment and care, and lead to poor HIV treatment outcomes (65, 69, 78). Several review papers in grey literature have summarized the relationships between food insecurity and HIV/AIDS (26, 54, 55). However, none have comprehensively considered the varying definitions and measures of food insecurity, or specifically explored the impacts of food insecurity on adverse HIV outcomes in the era of ART. Critical gaps in understanding remain regarding the relationships between food insecurity and HIV transmission, access to treatment and care, adherence to ART, pharmacokinetic effectiveness of ARVs, immunologic and virologic responses to ART, and survival. Understanding current evidence regarding the relationship between food insecurity and HIV outcomes, and gaps in knowledge, is essential to inform future research in this area. In the context of the current dissertation, elucidating the potential relationships between food insecurity and HIV outcomes will provide a theoretical basis from which to guide and interpret the proposed hypothesis-driven, empirical research in forthcoming Chapters.

The objective of this Chapter is to review current knowledge and gaps regarding the impacts of food insecurity on HIV-related risks and on HIV clinical outcomes in low and high resource settings. The Chapter begins with a review of salient definitions and measures of food insecurity, prevalence estimates in high and low resource settings, and impacts on general health outcomes. Applying the WFP’s conceptual framework of food insecurity, this Chapter will review evidence regarding the impacts of individual food
utilization and household food access on HIV outcomes (45), and draw on the conceptual framework proposed by Weiser et al. to delineate potential nutritional, mental health and behavioural pathways between food security and HIV (24).

2.3 Methods

The current literature review will employ a scoping review approach (79). Scoping reviews aim to map key concepts of a research area, its main sources, and thematic categorizes of evidence. This technique is considered particularly useful for examining complex topics that can only be reviewed by means of covering a broad range of literature (79). In contrast to systematic reviews, which seek to focus on a narrow topic and limit searches to specific study designs (i.e. randomized control trials), scoping reviews seek to identify all relevant literature to a topic regardless of study design (79). This approach to literature review was deemed appropriate for the task at hand given the breadth of each of the respective topics under study – that is, food insecurity (which constitutes food insufficiency, poor dietary diversity and poor food safety) and HIV outcomes (which includes HIV transmission, access to treatment and care, and ART outcomes).

A comprehensive literature search was performed including the following online databases: PubMed, OvidSP, Proquest and Psycinfo. Other literature sources included conference abstracts from the International AIDS Society (IAS), and grey literature from relevant multilateral agencies (e.g. WHO, UNAIDS, WFP, FAO, World Bank), bilateral agencies (United States Agency for International Development (USAID), European Union (EU) Commission), and academic literature from the International Food and Policy Research Institute (IFPRI). Given the broad definition of food insecurity, several keywords were used to extract articles on this topic: “food insecurity”, “food
insufficiency”, “dietary diversity”, “dietary quality”, and “food safety”. In light of the paucity of literature on these topics specific to HIV/AIDS, these searches were expanded to include review articles about nutrition, macronutrient deficiencies, micronutrient deficiencies, and food-borne diseases. In order to capture relevant literature on HIV/AIDS outcomes, these food security and nutrition keywords were combined with the following HIV-specific keywords: “HIV transmission”, “HIV treatment”, “HIV care”, “HIV and adherence”, “ART”, “ART”, and “antiretroviral”. In line with the *scoping review methodology*, the data extraction and analysis process involved compiling relevant findings into narrative descriptions and summarizing key findings in thematic categories (79).

2.4 Results

2.4.1 Definitions and Sub-components of Food Insecurity

Definitions of food insecurity have evolved considerably over the past half century, with literature citing over 200 definitions and 450 indicators (80). The UN’s WFP and FAO, multilateral agencies charged with the responsibility of global food aid and information systems (81), define food security as a state where “*all people, at all times, have physical, social and economic access to sufficient, safe and nutritious food that meets their dietary needs and food preferences for an active and healthy life*” (3). Implicit in this definition is that a person who is food insecure may experience food insufficiency, poor dietary quality or diversity, or poor food safety. Researchers in the US define food insecurity as additionally including an “*uncertain ability to acquire acceptable foods in socially acceptable ways*”. This definition suggests that food insecurity may constitute feelings of anxiety about the ability to access food, or procurement of food by activities
such as begging, relying on charity, scrounging, stealing, exchanging sex for food, and other illicit means (82).

Definitions and measures of the three main sub-components of food insecurity (food insufficiency, poor dietary diversity and poor food safety) vary significantly between different stakeholders, ranging from objective clinical or biological markers of nutritional and health status, to qualitative measures based on self-reports and subjective experience (83). Understanding and measuring the sub-components of food insecurity in the context of HIV requires consideration of the increased nutritional needs and altered physiological status of people living with HIV/AIDS.

**Food insufficiency**

Food insufficiency has been described in several ways in literature, depending on institutional background, ranging from objective clinical definitions of undernutrition to more subjective qualitative descriptions of hunger and resource shortages. For example, the WHO has defined food insufficiency in terms of clinical definitions of underweight based on BMI and anthropometrics (75, 84). The FAO and the EU both use the terms ‘food deprivation’, ‘undernourishment’ and ‘hunger’ interchangeably (3, 46), describing them as states where “caloric intake is below the minimum dietary energy requirement...needed for light activity and to maintain a minimum acceptable weight for attained height” (3). These organizations justify the interchangeable use of these terms on the basis that ‘food deprivation’ is merely a scientific term to denote ‘hunger’, which is “an uncomfortable or painful sensation caused by insufficient food energy consumption” (46). The USAID-funded Food and Nutrition Technical Assistance Project-2 (FANTA-2) project has defined food insufficiency or hunger in terms of having no food in the household, going to sleep hungry and skipping meals for 24 hours due to resource shortages (85). Epidemiologists have also defined food insufficiency in terms of hunger,
additionally emphasizing aspects of frequency and resources. For example, surveys
used in various North American settings have defined food insufficiency as a “condition
in which persons sometimes or often do not have enough food to eat” (86), as an
“inadequate amount of food intake due to a lack of resources” (87), and a state where an
individual is “sometimes or often hungry, but (does not) eat because (s/he) can’t afford
enough food” (88). Household definitions of food insufficiency describe it as a state
characterized by “restricted household food stores” or “too little food intake” among
adults or children in a household (89).

Defining and measuring food insufficiency in the context of HIV requires taking
into consideration HIV-positive individuals’ unique physiological and metabolic
requirements. Research suggests that people living with HIV have increased resting
energy expenditure (90, 91), which requires them to consume 10%-30% increased
energy/calories depending on their stage of progression, compared to an uninfected
individual (75, 92). Thresholds of what is a ‘sufficient’ or ‘insufficient’ amount of food for a
given individual will additionally vary depending on age, gender, physical activity level
and presence of co-infections (83). Certain groups require particularly elevated energy
intake, including pregnant and lactating women, children, persons with elevated physical
activity levels, and individuals co-infected with hepatitis C virus (HCV), tuberculosis (TB)
and malaria (83).

Poor Dietary Diversity

Dietary diversity has similarly been defined in varying ways in literature, ranging
from objective laboratory-based definitions of adequate macro and micronutrient status,
to culture- and context-specific descriptions of varied food intake. For example, the WHO
understands poor nutrient adequacy in terms of laboratory biomarkers of key vitamins
and minerals, such as Vitamin A and iron (93, 94). The FAO and EU define dietary
diversity as a “qualitative measure of food consumption that reflects household access to a variety of foods”, viewing this as a “proxy for nutrient adequacy of the diet of individuals” (95). The WFP and the IFPRI additionally describe dietary diversity in terms of the consumption of different food items or food groups over a specific period of time, which is not to be confused with frequency of consumption (96-98). Other definitions emphasize the fact that dietary diversity cannot be universally defined, as what constitutes ‘variety’ will differ across cultures, developmental stages, and contexts (99-101). At the individual level, dietary diversity reflects diet quality, mainly micronutrient adequacy of the diet (102), while at the household level, dietary diversity is usually considered as a measure of access to food (103), or of economic ability to consume a variety of foods (104).

Defining and measuring dietary quality and diversity among people living with HIV/AIDS is important in light of metabolic and physiologic processes associated with HIV, and must consider specific changes in nutrient utilization common in HIV disease progression and co-morbidities, as well as shifts caused by interactions with ART (83). For example, HIV-positive groups may experience losses in, or increased needs for, specific types of micronutrients depending on stage of HIV disease progression, pregnancy status, and co-infection (83).

**Poor Food Safety**

Although research on food insecurity has tended to focus on aspects of food insufficiency and dietary diversity, the WHO and FAO consider food safety to be an integral part of food security, and have developed several related definitions as part of their efforts to lead scientifically-based food standards and approaches to food safety (105). These organizations have defined food security as “the assurance that food will not cause harm to the consumer when it is prepared and/or eaten according to its
intended use” (106), and assume that it includes “contamination by chemical and biological agents and concerns about inherent food nature” (107). Food safety also pertains to the protection of the food supply from microbial, chemical and physical hazards that may be introduced at any stage of “food production, including growing, harvesting, processing, transporting, retailing, distributing, preparing, storing and consumption, in order to prevent foodborne illnesses” (108). Included in FAO and WHO understandings of food safety is the idea that foods should not be affected by adverse impacts of new food technologies, such as genetic engineering, irradiation of food, and modified-atmosphere packaging (109).

Defining and measuring food safety in the context of HIV requires consideration of HIV-positive individuals’ increased susceptibility to food-borne illness due to a weakened immune system. People living with HIV who contract food-borne illnesses often develop more severe symptoms, which can be recurrent and difficult to treat (110). Diarrhea is usually the most significant manifestation of food-borne infections and is a possible life-threatening complication and a major cause of morbidity in the pre-ART and post-ART eras (111). The major pathogens seen in AIDS-related diarrhea previously identified in the literature are cryptosporidium, microsporidium, salmonella, and cytomegalovirus (112). Other forms of food-borne illness are caused by natural toxins, moulds, and industrial contaminants (chemicals, rodents, unclean equipment) (113).

2.4.2 Measures and Indicators of Food Insecurity Among HIV-positive Individuals

A broad range of qualitative and quantitative tools exist to measure general food insecurity at the individual and household level (114). Despite their differences, contemporary food security measurement tools share certain similar features, including: a focus on quantifying inadequate access to food, rather than the population-level
availability and biological utilization of food; an emphasis on subjective measures of food insecurity, in addition to objective measures; and a reliance on tangible measures of food insecurity, rather than proxies (115). The most widely used and validated instruments for measuring food insecurity are the US Household Food Security Survey Module (US-HFSSM), the Household Food Insecurity Access Scale (HFIAS) and the Radimer/Cornell measure (82). More recently, FANTA-2 developed a household hunger scale, which has been validated cross-culturally to measure the ‘food insufficiency’ component of food insecurity (116).

These tools have been commonly used to measure food insecurity among people living with HIV/AIDS. However, none have been validated for use in HIV-positive populations (83). Use and validation of food security measurement tools in the context of HIV requires consideration of the unique biological and physiological interactions associated with HIV illness and disease progression, ART use, the global emergence of ‘overnutrition’, and risk factors specific to women, children, and people with addictions and co-infections (83). In the absence of validated tools to measure food insecurity among people living with HIV/AIDS, many researchers have applied either qualitative measures of food insecurity or objective, clinical markers of nutritional status.

Efforts are currently underway to harmonize food insecurity measures for application in HIV-affected populations between key international stakeholders, including the WHO, WFP, FAO, USAID and PEPFAR. This initiative holds promise for the development of harmonized measures of general food insecurity, despite challenges related to cultural and contextual variations between populations (117). In particular, advancement has been made to harmonize measures of sub-components of food insecurity. Regarding the ‘food insufficiency’ component of food insecurity, international stakeholders collaboratively developed and cross-culturally validated a Household Hunger Scale (HSS) (116), which has been extensively tested in HIV-endemic countries
As a surrogate measure of food insufficiency, these organizations have additionally agreed on clinical definitions of ‘nutrient insecurity’, which includes specific cut-offs for undernutrition, based on BMI and other anthropometrics for specific HIV-vulnerable groups, notably pregnant and lactating women, children and infants (118).

In terms of the ‘dietary diversity’ component of food insecurity, the FAO and EU have developed a harmonized qualitative tool to measure dietary diversity at the individual and household level, and instructions for culture-specific adaptation. The dietary diversity tools provide a rapid, user-friendly and low cost alternative to clinical and biomarker techniques for measuring household access to varied food and individual nutrient adequacy (103). International organizations have agreed on threshold values for the laboratory and clinical measurement of micronutrient undernutrition (119), which is a surrogate measure of poor dietary diversity. Cut-off values have been established for hemoglobin concentration, for example, which is the most widely used indicator for assessing programmatic impact of micronutrient interventions (119). International organizations commonly defer to measures of ‘overnutrition’, another surrogate measure of poor dietary diversity, based on BMI (120).

Finally, efforts are underway to harmonize the quantitative measurement of food safety hazards, which would enable assessment of the ‘food safety’ component of food insecurity. Of the existing qualitative and quantitative food safety measures (121), only one has been validated for use in HIV-positive populations or endemic settings (122). The WHO and FAO are standardizing measures of food-borne diseases (123) as surrogates of biological contamination of food, and measures acceptable daily intakes of pesticide residue, as surrogates of chemical food safety (124).
2.4.3 Prevalence and Correlates of Food Insecurity Among People Living With HIV/AIDS

Food insecurity is highly prevalent and well above general population estimates among people living with HIV/AIDS in both low and high resource contexts. A study in BC, Canada, found that 48% of individuals receiving ART through the free provincial health care system were food insecure, which is approximately five times the prevalence of the general Canadian population. Twenty-one percent of respondents indicated the presence of food insecurity with hunger, the most severe category of food insecurity (56). Approximately 65% of HIV at-risk IDU in the same province reported frequent hunger and either an inability to afford food, or the purchase of drugs instead of food (68). Similarly, in a sample of HIV-positive homeless and marginally housed individuals in San Francisco, California, over half were estimated to be food insecure, nearly five times the prevalence of US national estimates (125). Recent studies among people living with HIV in Miami, Florida and Atlanta, Georgia found that 30% reported being hungry and not being able to afford enough food (64). Among HIV-positive crack-cocaine users in the same settings, 34% reported not eating, or barely eating, for two or more days in the previous month (38).

In resource-limited settings, ecologic data demonstrates that the prevalence of undernutrition and micronutrient deficiencies (markers of severe, chronic food insufficiency and poor dietary diversity) are elevated in many HIV-affected populations. In most sub-Saharan African countries with generalized HIV epidemics, the proportion of stunting and underweight among children <5 years exceeds 35% and 15%, respectively (Table 2.1), while the prevalence of anaemia (a proxy for iron deficiency) and Vitamin A deficiency among children <5 years and pregnant women is consistently moderate or severe (Table 2.2). Cross-sectional studies in select countries provide additional insights.
into food insecurity among people living with HIV in resource limited settings. A recent summary of 67,038 individuals enrolling in HIV care programs at Academic Model Providing Access to Healthcare (AMPATH) clinics in western Kenya reported that 33.5% of enrollees were food insecure, with a range from 20% to 50% depending on clinic site (126). A cohort study of 456 HIV-positive adults in rural Uganda found that 74.6% reported any degree of food insecurity and 37.9% reported severe food insecurity at baseline (127). A separate Ugandan survey of 144 households involving primarily HIV-infected women found that 59% had low dietary diversity, and 44% were accessing food aid. HIV-affected households coped with food insecurity by reducing household meal portion sizes on a daily basis and selling non-productive household assets (128). A systematic sample of 67 HIV-positive adults in Lake Victoria in Kenya found that all participants were food insecure, with 79.1% reporting severe food insecurity (129).

A consistent theme in both resource rich and limited settings that has emerged is a significant inequity in the experience of food insecurity by gender, with women being most at risk (56, 77, 127). For example, among a sample of HIV-infected individuals in BC, 33% of women were categorized as hungry compared to 20% of men (56). In a sample of HIV-positive adults in Uganda, women were significantly more likely to be severely food insecure at baseline (41.7% vs. 28.8%) (127). In addition to gender, poverty and indicators of low socio-economic status including unemployment, unstable housing and lack of health insurance have been strongly correlated with food insecurity among HIV-infected individuals (38, 56, 69, 125). Drug use has also been a consistent correlate of food insecurity in HIV-infected populations in BC, San Francisco, Miami, and Atlanta (56, 64, 130, 131). Additional correlates of food insecurity include living with recent incarceration, and worse physical and mental health status (56, 125). In BC, Uganda and Kenya, having children and other dependents has been significantly associated with household food insecurity among HIV-infected individuals (56, 128,
Additional research is warranted in both high- and low-resource settings to better understand and address the presence and correlates of food insecurity in diverse HIV-infected population groups.

2.4.4 Impact of Food Insecurity on General Health Outcomes

Food insecurity can affect health directly or indirectly through the impact of poor nutritional status (132), or through social and behavioural mechanisms that influence choices and behaviours (86). Food insecurity is associated with adverse health outcomes for several diseases other than HIV. Food insecurity has been associated with poor mental health status among adults and adolescents, including symptoms of depression, dysthymia, and suicide (86, 89, 127). Food insecurity has been associated with elevated rates of obesity, diabetes, hypertension and heart disease (133-136). Many of these associations persist even after controlling for measures of socio-economic status (89, 134, 135). A study among 11,539 children in the US suggests that a dose-response relationship may exist between food insecurity and poor health outcomes (137). Additional research is needed to investigate the extent to which food insecurity contributes to metabolic and cardiovascular complications of HIV. This research is particularly important in light of the increasing contribution of cardiovascular and metabolic complications of HIV to overall morbidity and mortality among HIV-infected individuals (138).
2.4.5 Impact of Food Insecurity on HIV Transmission Risk

*Horizontal Transmission of HIV*

In many parts of the world, women may lack authority to manage household resources, including food procurement (26, 55). At the same time, they are invariably responsible for feeding household members, notably children and the infirm (26). As a coping mechanism, women may become involved in sex work or intergenerational relationships to gain access to food-related resources, where they lose the ability to negotiate safe sex practices (55, 139). South African women who reported hunger were more likely to engage in transactional sex (140). Similar findings were reported in Nigeria, where 35% of female sex workers said that poverty and lack of means to obtain food caused them to engage in sex work, and to engage in unprotected sex with clients (141). A population-based survey in Swaziland and Botswana found that women reporting food insufficiency in the past 12 months had 80% increased odds of selling sex for money or resources, 70% increased odds of engaging in unprotected sex and reporting lack of sexual control, and 50% increased odds of intergenerational sex (77). These associations remained even when controlling for other markers of socioeconomic status. Similar findings were identified in BC, Canada, where a study of HIV-positive IDU found self-reported frequent hunger was significantly associated with unprotected sex in the last 6 months (37).

In addition to risky sex, food insecurity may also increase vulnerability to HIV through other mechanisms. For instance, in a population-based case-control study of African-American men and women conducted in North Carolina, US, food insufficiency was found to be associated with heterosexually acquired HIV infection, both in the complete study population and in the subset without identifiable high-risk sexual behaviour (142). This may occur because food insecurity can lead to malnutrition, which
heightens risk of HIV transmission by compromising immunostatus as well as gut and genital mucosal integrity (55). Food insecurity has also been associated with unsuppressed viral loads among those receiving ART (69), which may heighten risk of HIV transmission via vertical, sexual and drug-using routes (143).

No current studies have examined the relationship between food insecurity and HIV transmission risk longitudinally. Longitudinal data using scaled, validated measures will permit a better understanding of the causal pathways and mediating factors in this relationship and how they are modified by gender. Investigations into household food insecurity and transmission among sero-discordant couples or within social networks could also shed light on this topic. More studies are needed to evaluate whether food insecurity may predispose people to HIV transmission through mechanisms other than risky sex. For example, research is needed to examine the relationship between food insecurity and unsafe injection practices among HIV-infected individuals. Food insecurity may indirectly influence needle-sharing behaviour by compromising IDUs’ ability to access health care and social support services, including access to safe injection education and clean syringes. Research is also needed to assess the role of targeted food assistance and income generation programs in decreasing HIV transmission risk, particularly for women who appear to bear the greatest burden.

*Vertical Transmission of HIV*

While there is limited literature on the specific impact of food insecurity on MTCT, parallel literature linking poor dietary diversity, malnutrition and micronutrient deficiencies to MTCT does exist. Food insecurity may represent a proximal risk to many of these nutritional and micronutrient deficiencies, thus predisposing risk of MTCT. Insufficient micronutrient intake and poor dietary diversity have been associated with elevated risk of MTCT. Among women with severe and moderate iron deficiency, 28% and 16% had
transmitted HIV to their infants by the end of 6 weeks (144). Several observational studies have found that low vitamin A levels in pregnant women also increase risk of MTCT (145). Low maternal BMI and low middle upper arm circumference, which are measures of malnutrition, have each been associated with intra- and early post-partum MTCT (146). Maternal weight loss during the second trimester of pregnancy has been associated with a 2.3-fold increased risk of intrapartum MTCT, and weight loss during the third trimester correlated with a 1.7 increased risk of postpartum transmission (147). Food insecurity may represent a measurable, modifiable and early marker of maternal and fetal risk. Studies are needed to directly evaluate relationships between food insecurity and MTCT, and the mechanisms through which food insecurity might increase risk of MTCT.

### 2.4.6 Impact of Food Insecurity on Access to HIV Treatment and Care Services

Food insecurity is a barrier to accessing health care in both resource rich and resource poor settings. In the US, food insecurity has been associated with postponing needed medications and care, and increased emergency department use and hospitalizations (134, 137, 148). In a survey of 100 households in rural Gabon, poor nutritional status among children aged 0-23 months was associated with limited access to health care services (149). Among 2,889 households surveyed in Eastern Burma, 4.1% of Karen, 2.0% of Karenni and 26.6% of Shan experienced food security-related violations (i.e. theft and/or destruction of food supplies). Women in households experiencing violations related to food insecurity exhibited decreased access to antenatal interventions (150). Such findings highlight the potential for ethnic and gender-based inequalities both in the experience of food insecurity and its potential impact on access to essential medical care.
A number of qualitative studies have evaluated the specific impact of food insecurity on access to treatment and care services among HIV-infected populations. A recent study among HIV-positive individuals in Miami and Atlanta found that people who were food insecure were over four times more likely to report not being able to afford the cost of ARVs, and almost five times more likely to report not getting to a clinic or doctor due to lack of transportation (64). In a qualitative study in Tanzania, hunger and household food insufficiency were cited by respondents as significant concerns regarding access to HIV health services. Reluctance to initiate ART was associated with anxiety regarding being able to maintain consumption of sufficient food and a balanced diet (151). A qualitative study conducted in an urban Kenya slum found that fear of taking medication on an empty stomach due to lack of food was a widely cited reason for refusing to take ARVs, despite ART clinical eligibility and free access to treatment and care (152). Among individuals with low income in many parts of the world, accessing health care services must be balanced against competing demands for food and other resources. In India, being unemployed and having a lower income were both associated with not accessing ART among HIV-infected individuals (153). In a qualitative study in Uganda, individuals receiving free ARV medications often had to choose between using their limited income to pay for transportation to the clinic versus being able to adequately feed themselves and their children (154). As a result of these impossible choices, some individuals in this study either missed health care appointments or were unable to pick up their ARV medications. These qualitative studies all suggest that food insecurity has an adverse impact on ART access and uptake. There is now a need to quantify the extent of this relationship, and to identify the context-specific mechanisms capable of mitigating this adverse impact of food insecurity on ART outcomes.
2.4.7 Impact of Food Insecurity on ART Outcomes

Adherence to ART

Several qualitative studies undertaken in sub-Saharan Africa have identified food insecurity as a risk factor for non-adherence to ARVs. Among patients surveyed in Rwanda, 76% described fear of “having too much appetite and not enough to eat” as a major obstacle to their ART adherence. In contrast, concerns about drug toxicities, disruption of the daily routine, and acceptance of their HIV illness were of concern to only a minority of participants (78). In a conflict-affected population in Northeastern Uganda, individuals consuming only one meal a day and those dependant on caregivers for food were particularly prone to missing ART doses (155). In Zambia, the belief that ARVs must be taken with food has led individuals to skip doses in the absence of available or accessible food (156). The impact of food insecurity on adherence is not limited to developing countries. In BC, Canada, individuals who were food insecure had over two times the odds of being less than 95% adherent to treatment, compared to individuals who were food secure (157). In San Francisco, food insecurity and ART non-adherence were associated in a non-linear manner. Participants with severe food insecurity were less likely to be >80% adherent to ART than were those who were not severely food insecure (69). A sub-analysis including 208 HIV-positive individuals in Miami and Atlanta found that food insufficiency was independently associated with both <80% and <90% adherence to ART (64).

Some recent research demonstrates a strong positive impact of nutritional support on ARV adherence and retention in care. An ecological analysis of 177 HIV treatment and care sites supported by PEPFAR across seven sub-Saharan African countries found that access to nutrition support services was the strongest predictor of non-attrition from HIV treatment (158). A qualitative study in Kenya found that ARV...
patients enrolled in a food support program self-reported greater ARV adherence than those not receiving nutritional support (159). In 2004, a pilot study of the effect of food supplementation on ARV adherence was initiated in Zambia with the support of the Zambian Ministry of Health and the UN's WFP. In adjusted analyses, individuals receiving food supplementation had higher levels of adherence as recorded using a variation of the medication possession ratio (MPR). Two hundred fifty-eight of 366 (70%) patients in the food supplementation group achieved an MPR of 95% or greater compared to 79 of 166 (48%) among controls (160). This intervention study is an important first step in investigating the impacts of food supplementation to food insecure individuals on ART use. Additional operational and clinical research is urgently needed to assess the benefits of food security interventions for patients receiving HIV treatment.

**Pharmacokinetics of antiretrovirals**

Several studies have found that the absence of food adversely impacts the pharmacokinetic efficacy of PI-based regimens (161, 162). Studies focused on Darunavir have shown that drug intake without food results in a 30% decrease in drug plasma concentration (162). The impact of food intake on bioavailability has also been noted for other protease inhibitors. The bioavailability of Saquinavir, Nelfinavir, Liponavir/Ritonavir, and Atazanavir have been found to increase by 700%, 200-300%, 48-97% and 35%, respectively, when taken with food, compared with a fasted state (161). As a result of pharmacokinetic impacts, it is possible that food insecurity may contribute to reduced treatment effectiveness. Studies are needed to specifically evaluate this, particularly as availability of second-line regimens increases in low resource settings.
**Immunologic outcomes**

Several studies have assessed associations between food security and immunologic status. In BC, individuals reporting food insecurity had significantly lower CD4 counts at ART initiation, compared to food secure individuals (56). Food insecurity was also associated with lower CD4 cell counts among HIV-infected individuals in San Francisco (125). As these studies were cross-sectional, the direction of causality is not known. A recent longitudinal analysis of 275 adults receiving ART in the Boston and Providence area found that having at least one episode of food insecurity was significantly associated with reduced CD4 cell count improvement, compared to being consistently food secure (163). Studies from the pre-ART era show strong associations between malnutrition and immunologic decline (164, 165), but none of these studies specifically focused on food insecurity. In a large randomized controlled trial of HIV-infected pregnant women, micronutrient supplementation was found to significantly elevate CD4 cell counts (166). However, a recent food supplementation pilot study among food insecure adults in Zambia did not show additional increases in CD4 counts at 6 or 12 months in individuals initiating antiretroviral therapy (160). Additional research is needed to clarify the impact of food insecurity on absolute CD4 cell count and CD4 cell count decline pre-ART, and on potential immunologic recovery after ART initiation.

**Virologic outcomes**

In a recent study among 2,353 HIV-infected individuals receiving ART, food insecurity was associated with a 1.37 increased odds of having unsuppressed HIV RNA. Mediation analysis in this study further found that neither ART adherence nor BMI contributed to the association between food insecurity and virologic non-suppression (167). In a study among HIV-infected homeless and marginally housed individuals on ART in San Francisco, food insecurity was found to be associated with
incomplete HIV RNA suppression. (69) In this study, the odds of viral suppression was 70% lower among participants who reported severe food insecurity, compared to those who were food secure or had only mild or moderate food insecurity even after adjusting for non-adherence. (69) The authors also looked at separate models stratified by high versus low levels of adherence, and found that the effects of food insecurity on viral load suppression were more pronounced among less adherent individuals. Finally, the authors looked at associations between food insecurity and viral load suppression stratified by regimen type. They found that for participants on protease inhibitor-based regimens, the association between food insecurity and viral load suppression was similar to that in the entire sample, and the study was underpowered to look at this association for participants on NNRTI-based regimens. They concluded that the impact of food insecurity on viral suppression may be due to the combined effect of behavioural and biologic mechanisms that lead to suboptimal drug levels required for viral suppression. Another cross-sectional study among 209 individuals receiving ART in Atlanta similarly found that food insufficiency was associated with a decreased likelihood of having an undetectable viral load. However, a major limitation of this study is that it did not explore the independent association between these factors, controlling for potential confounders (64), therefore it is possible that this observed association was a spurious one. In contrast to these studies, a sub-analysis of 47 HIV-positive crack-users receiving ART in Miami and Atlanta found no significant relationship between food insufficiency and virologic suppression in univariate analysis (38); however, the study was limited by its small sample size, and underpowered to examine this association. Future research should further examine the mechanistic pathways of suboptimal viral suppression among food insecure individuals on ART.
**Survival**

While there is limited literature looking at specific impacts of food insecurity on mortality, studies from resource rich and resource poor settings show strong associations between markers of poor nutritional status and mortality among ART treated patients (55, 168, 169). One recent study found that food insecurity has an adverse impact on the survival of individuals living with HIV/AIDS. In a longitudinal cohort study of 1,119 individuals receiving ART in BC, Canada, individuals who were food insecure and underweight (BMI<18.5 kg/m$^2$) were two times more likely to die over an eight year follow-up period compared to those who were neither food insecure nor underweight. This relationship remained statistically significant after controlling for adherence, baseline CD4 counts, substance use, and socioeconomic variables (65). There was also a trend towards increased risk of mortality among people who were food insecure but had normal weights, but not among people who were food insecure and underweight. More studies from both resource rich and resource poor settings are needed to confirm these relationships, and to better understand the extent to which associations between food insecurity and mortality are mediated by malnutrition versus other biologic and behavioral mechanisms.

### 2.5 Discussion

This Chapter has reviewed salient definitions of food insecurity and its sub-components (food insufficiency (or hunger), poor dietary diversity, and poor food safety) and described existing considerations and tools for its measurement.
It presented emerging evidence on the role of food insecurity in HIV prevention, treatment and care. Specifically, it highlighted HIV-positive groups that are most affected by food insecurity, and provided evidence that food insecurity increases risk of HIV transmission, impedes access to HIV treatment and care services, and is associated with worse clinical outcomes for individuals receiving ART including reduced adherence to ART, decreased pharmacokinetic efficacy of ARVs, poor immunologic and virologic response to ART, and reduced survival.

Recognizing the inter-relationship between food security and HIV, international multilateral and bilateral organizations now consider the integration of nutrition interventions into HIV/AIDS treatment and care programs as a ‘standard of care’ (75, 170-172). As countries and communities put these policies and program guidelines into practice, there is a need to address critical gaps in the understanding of the context-specific determinants of food insecurity, and the impact of food insecurity on risk of HIV transmission and on clinical outcomes in both high and low resource settings. For example, while studies have found a strong link between food insecurity and sexual risk-taking behaviours, few have employed validated scales, and none have examined these relationships longitudinally. No studies to date have examined whether food insecurity increases needle sharing among HIV-infected IDU, or whether food insecurity specifically predisposes to increased risk of MTCT of HIV. In addition, there is a need to identify the pathways that prevent food insecure individuals from accessing HIV treatment and care, and from adhering to ART regimens. Longitudinal research is critical to clarify the relationship between food insecurity and immunologic, virologic and mortality outcomes. Finally, research evaluating the impacts of targeted food assistance, sustainable livelihood strategies and income generation programs on food insecurity’s contribution to HIV transmission risk, access to care, and HIV clinical outcomes are urgently needed in high- and low-resource settings.
However, gaps in evidence about the interaction between HIV/AIDS and food insecurity should not impede efforts to expand nutritional and livelihood support to people living with HIV/AIDS. There is a need to “learn-by-doing”, and to integrate operational research into programmatic responses to these overlapping epidemics in order to identify effective, sustainable and context-specific food insecurity interventions for people living with HIV/AIDS. Particularly, as global efforts are underway to expand HIV treatment access to clinically eligible individuals, there is an imperative to ensure the food security needs of people living with HIV/AIDS are being met, and to evaluate the impacts of different support paradigms on individual and public health HIV outcomes.

As background to the empirical studies in this dissertation, this Chapter reviewed current evidence and gaps in knowledge regarding the impacts of food insecurity on HIV outcomes. Of relevance to this dissertation, this Chapter described a growing body of evidence regarding the relationship between food insecurity and adverse HIV outcomes specifically among illicit drug users in high resource settings. Findings from this review provide supporting mechanistic pathways described in the adapted risk environment conceptual framework (Section 1.5.5) which will be applied in subsequent Chapters, and provide a knowledge-base from which to interpret and contextualize forthcoming empirical study results.
Table 2.1 Prevalence of stunting and underweight among children under 5 years in sub-Saharan African countries with generalized HIV epidemics

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<td>Gabon</td>
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</tr>
<tr>
<td>Equatorial Guinea</td>
<td>5.0</td>
<td>35.0</td>
<td>19.0</td>
</tr>
</tbody>
</table>

2. Stunting defined by World Health Organization (WHO) as: minus two standard deviations from median height-for-age according to WHO Child Growth Standards (174)
3. Underweight defined by WHO as: minus two standard deviations from median weight-for-age according to WHO Child Growth Standards (175)
Table 2.2 Prevalence of anaemia and Vitamin A deficiency among women and children under 5 years in sub-Saharan African countries with generalized HIV epidemics

<table>
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<td>Equatorial Guinea</td>
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<td>41.7</td>
<td>40.8</td>
<td>16.5</td>
<td>13.9</td>
</tr>
</tbody>
</table>

2. Anaemia defined by World Health Organization (WHO) as: Hb<110 g/L (176)
3. Vitamin A deficiency defined by WHO as: serum retinol <0.70 µmol/l (176)
CHAPTER 3: PREVALENCE AND CORRELATES OF FOOD INSECURITY AMONG HIV-
POSITIVE INDIVIDUALS RECEIVING ART ACROSS BC, CANADA

3.1 Synopsis

**Background:** Elevated prevalence of food insecurity has been observed among people living with HIV/AIDS in high-resource settings, including in BC. Shifts in the micro and meso risk environment of HIV-positive individuals in BC over the past decade may have increased vulnerability to food insecurity and associated adverse HIV treatment outcomes. **Methods:** The objective of Chapter 3 is to assess, through cross-sectional analyses, the prevalence and correlates of food insecurity among hard-to-reach HIV-positive adults receiving ART across BC in the LISA cohort. Food insecurity was measured using the Radimer/Cornell scale. Bivariate analyses were performed to identify socio-demographic, behavioral and clinical characteristics associated with food insecurity. A multivariable logistic regression explanatory model was used to identify factors independently associated with food insecurity. **Results:** Among 457 participants interviewed in 2007/08, 324 (71.0%) were classified as food insecure. In adjusted analyses, individuals who were younger (adjusted odds ratio [AOR] = 0.95, 95% CI: 0.92 - 0.98), had an annual income <$15,000 (AOR = 3.15, 95% CI: 1.83 - 5.44), smoked tobacco (AOR = 2.30, 95% CI: 1.30 - 4.07), ever used illicit drugs (AOR = 1.85, 95% CI: 1.03 - 3.33), and had current depressive symptoms (AOR = 2.34, 95% CI 1.38, 3.96) had significantly increased odds of being food insecure. **Discussion:** The prevalence of food insecurity among hard-to-reach HIV-positive individuals receiving ART in BC was alarmingly high, and was associated with specific socio-demographic, behavioral and clinical factors. These findings suggest a need to further examine the potential relationship between food insecurity and adverse HIV outcomes among specific vulnerable groups, notably among illicit drug users.
3.2 Introduction

An estimated 9% of Canadian and 11% of US households were estimated to be food insecure in 2004 and 2005, respectively (177-179). Studies in North America have found that food insecurity is most common among women, people of Aboriginal descent, and individuals with low-income, unstable housing, mental illness, and a history of tobacco and illicit drug use (177, 180-182). Significant levels of food insecurity have also been documented among immune-compromised populations in North America, including the elderly and people living with HIV/AIDS (56, 183). A study among HIV-positive homeless and marginally housed individuals in San Francisco found that approximately 54% were food insecure (125). Recent studies in Miami and Atlanta found that 30% of HIV-positive individuals experienced hunger, or food insufficiency (64).

In BC, a study assessing the prevalence of food insecurity among 1,213 individuals newly receiving ART in 1998/1999 found that 48% of individuals were food insecure, and 21% were hungry (56). These findings suggested that food utilization and access in this population were alarmingly poor. Since this study was conducted, the province and notably Metropolitan Vancouver have undergone substantial socio-demographic and economic changes that have caused vulnerable groups to become further marginalized (57). Metropolitan Vancouver, which is home to the majority of people living with HIV/AIDS, is characterized by a growing gap between rich and poor (58) and a shift in the risk environment of specific vulnerable groups. Over recent years, Vancouver has witnessed an increase in homelessness (184), displacement of illicit-drug using populations from healthcare services (60) and elevated dependence on social services, including food banks (57).

The impacts of these social and structural changes on the food security of people living with HIV/AIDS remain unknown. Understanding the current burden of food insecurity in this population and factors associated with it is essential in light of evidence that food insecurity is associated with various forms of malnutrition (185-188), and also with obesity, diabetes and
heart disease (86, 133, 189). It is particularly important given evidence regarding the relationship between food insecurity and risk of HIV transmission, delayed HIV treatment, non-adherence to ART, poor immunologic and virologic response, and higher risk of mortality (presented in Chapter 2). This study therefore sought to examine the current prevalence and independent socio-demographic, behavioural and clinical characteristics associated with food insecurity among individuals newly receiving ART across BC.

3.3 Methods

3.3.1 Study Sample: LISA

Socio-demographic and behavioral survey data for this analysis were obtained through the BC-wide LISA cohort, and linked to clinical and laboratory data contained in the provincial HIV/AIDS DTP administrative database. Eligibility criteria, sampling and recruitment procedures for these cohorts are described in detail in Sections 1.8.1 and 1.8.3. Briefly, LISA was designed to over-sample hard-to-reach populations across BC, and recruited adults who are aged 19 years or older, residents of BC and who have previously accessed ART.

3.3.2 Outcome Variable

In this cross-sectional analysis, food insecurity was used as our primary dependent variable. Food insecurity was measured at the household and individual (adult) level using an abbreviated version of the Radimer/Cornell scale (88, 190). As recommended by Kendall et al. (190), individuals were categorized as food insecure if they gave a minimum of one positive answer (often/sometimes) to any one of the eight items measuring household or individual (adult) food insecurity.
The Radimer/Cornell scale covers topics such as insufficient food intake, the physical sensation of hunger, problems with household food supply, diet quality, anxiety related to food insecurity, and efforts made to maintain household food supplies (88, 190). It has shown to be a valid measure of food insecurity and hunger on the basis of several criteria (191). Radimer/Cornell measures have been validated in diverse North American settings, including among low-income groups, households with women and children, urban and rural settings, and diverse ethnic and age groups (192-194), and in cross-cultural settings internationally (195, 196). The Radimer/Cornell tool and a detailed description of validation studies of the tool are described in Appendix 2.

3.3.3 Potential Explanatory Variables

Socio-demographic

Potential covariates were identified for inclusion in analysis through review of findings from previous studies assessing food insecurity in HIV-infected populations. In addition to age and gender, variables found to be previously associated with food insecurity in univariate analyses in BC have included: Aboriginal ancestry (yes vs. no), financial dependents (yes vs. no; dependents defined as children, partner, roommate, other), current unstable housing (yes vs. no; unstable housing defined as residing in a shelter, hostel, treatment centre, recovery house, jail, or having no fixed address), high school graduation or higher (yes vs. no), and annual income (≥CAD$15,000 vs. <CAD$15,000) (56). Given the high HIV prevalence and extreme social marginalization experienced by individuals living in Vancouver’s downtown eastside (DTES), compared to other areas in the province (58, 197, 198), the analysis considered current residency in the DTES (yes vs. no) as an additional potential explanatory variable.
**Behavioural**

Three substance abuse variables were included in the analysis, namely current tobacco use (yes vs. no), current illicit drug use (yes vs. no), and lifetime alcohol dependency (yes vs. no). These have been previously reported to be associated with food insecurity among HIV-infected individuals in Canada and the US (56, 64, 125). Illicit drug use was defined as consumption of cocaine, heroine, speedball, and/or crystal methamphetamine. Alcohol dependency was defined using the CAGE questionnaire, which identifies participants as alcohol dependent if they answer ‘yes’ to two or more of CAGE’s four questions (199).

**Clinical**

Clinical variables previously found to be associated with food insecurity in high resource settings (69, 125, 200) were also included in the analysis, including: current body-mass index (BMI) (median; defined as weight (kg) divided by height (m²)); self-reported adherence (yes vs. no; adherence defined by Kerr et al. (201), and categorized as ≥95% adherence, <95% adherence) within a one month recall period prior to interview; CD4 cell count (cells/mm³) and HIV viral load (Log_{10} copies/mL) measurements within three months of the interview date. CD4 cell count was recorded using flow cytometry and fluorescent monoclonal antibody analysis (Beckman Coulter, Inc., Mississauga, Ontario, Canada), and HIV viral load was measured using the Roche Amplicor Monitor assay (Roche Diagnostics, Laval, Quebec, Canada) using either the standard method or the ultrasensitive adaptation. Finally, we included depressive symptoms as a potential explanatory variable (defined using the 10-item Center for Epidemiological Studies Depression scale (CES-D 10). Participants with scores of 10 or higher were identified as having depressive symptoms. This scale has been shown to have good predictive accuracy when compared to the 20-item scale (kappa = 0.97, p <0.0001) (202). This variable was included because previous studies have found significant associations between food insecurity and symptoms of depression in non-HIV infected populations (203, 204), and because few
studies have evaluated the relationship between these variables in HIV-infected populations despite elevated reported prevalence of each condition (56, 205, 206).

3.3.4 Statistical Analyses

Bivariate analyses were performed to determine differences between explanatory variables for individuals who were food secure and food insecure. Chi-square Tests were used to compare categorical variables. In instances where counts were small (five or less), the Fisher's Exact Test was used. Continuous variables were compared using Wilcoxon Rank Sum Test. Multivariate logistic regression was performed to determine independent predictors of food insecurity. A backward-selection procedure based on the Akaike Information Criterion was used to select variables for inclusion in the final model (207). The Concordance Index was used to determine the final model fit (208). Tolerance and Variance Inflation Factor values were calculated to assess possible multicollinearity of explanatory variables in the final model (209). All analyses were conducted using SAS version 8.1.3 (SAS Institute, Cary, North Carolina, United States of America). All tests of significance were two-sided, with a p-value less than 0.05, or 95% CI not overlapping 1.0, indicating a statistically significant association.

3.4 Results

Between July 1, 2007 and June 30, 2008, 457 individuals had enrolled in the LISA study. A total of 324 (71.0%) participants reported being food insecure, and 168 (36.8%) reported being hungry. Among food insecure individuals, 246 (75.9%) had accessed a grocery, food bank or meal program in the last three months. Table 3.1 shows participant responses to individual food security items used in the Radimer/Cornell food insecurity scale. Among all participants, 58.0% claimed that they often/sometimes felt anxious about running out of food, and 60.6% worried about affording sufficient food; 56.5% claimed their food often/sometimes
does not last and they do not have enough money to buy more; and 57.3% reported running out of food to make a meal and not having enough money to buy more.

Results from bivariate analyses of socio-demographic, behavioural and clinical characteristics associated with food insecurity in the LISA sample are presented in Table 3.2. The median age of participants was 46 years (IQR: 41 - 52), 342 (74.8%) were male, and 150 (32.8%) reported Aboriginal ancestry. Socio-demographic and behavioural characteristics associated with food insecurity included being younger, Aboriginal, heterosexual, having less than high school education, living in Vancouver’s DTES, having unstable housing, lower annual income, illicit drug use, alcohol dependency and tobacco smoking ($p <0.001$). Clinical factors significantly associated with food insecurity included having a lower BMI, depressive symptoms, <95% adherence to ART, lower median CD4 cell count, and higher median HIV viral load ($p <0.001$).

Table 3.3 shows unadjusted and adjusted results of factors associated with food insecurity. In adjusted models, factors significantly associated with food security included younger age (AOR = 0.95, 95% CI: 0.92 - 0.98), an annual income below $CAD15,000 (AOR = 3.15, 95% CI: 1.83 - 5.44), illicit drug use (AOR 1.85, 95% CI: 1.03 - 3.33), tobacco smoking (AOR 2.30, 95% CI: 1.30 - 4.07), and depressive symptoms (AOR 2.34, 95% CI: 1.38 - 3.96). Food insecurity was marginally associated with lower BMI (AOR 0.94, 95% CI: 0.88 - 1.01). The goodness of fit for the final model was assessed by the concordance Index ($c = 0.825$), which suggested no indication of lack of fit. The variance inflation factor (VIF) was examined for each variable, all of which were less than 1.33, respectively. These values indicate that there were no concerns with multicollinearity of explanatory variables in the final model.

### 3.5 Discussion

This analysis found that 71% of individuals in a sample of HIV-positive individuals exposed to ART across BC were food insecure, and that food insecurity was associated with a
compendium of socio-demographic, behavioral and clinical characteristics. The prevalence of food insecurity in this cohort was approximately seven times higher than that of the Canadian general population (177), and approximately 23% higher than reported in a study of HIV-infected individuals receiving ART in BC 10 years earlier (56). Food insecurity among HIV-infected individuals on ART in BC was also approximately 20% higher than homeless and marginally housed individuals on ART in San Francisco (69).

The severity of food insecurity identified in this cohort may be partially explained by the increased socio-economic marginalization of Vancouver’s HIV-positive population. Approximately 40% of food insecure individuals in this cohort reside in the DTES of Vancouver, a post-industrial neighborhood known for its extreme poverty, high rates of unstable housing, and prevalent drug use (198). This study found that food insecurity was significantly associated with low annual income, consistent with the socio-demographic profile of Vancouver’s DTES. A recent study of HIV-infected residents in this neighborhood found that 70% of HIV-infected ART recipients live below the Canadian poverty line, and nearly 90% do not have post-secondary education (197). Studies evaluating food insecurity among non-HIV infected North Americans have similarly reported associations between poor nutritional status and low income and education levels (180, 186, 210, 211). Findings from the current analysis were consistent with these, and with a study in BC among HIV-infected individuals conducted 10 years earlier (56). Follow-up studies should evaluate the extent to which this population is accessing social support services, and whether they have any positive mitigating impact on food insecurity.

Fifty-seven percent of illicit drug users in this study sample reported food insecurity, compared to 16% ten years ago (56), representing an over three-fold increase in prevalence of food insecurity. This may be partially explained by a shift in the broader micro/meso socio-structural and physical risk environment of drug users. Gentrification of Metropolitan Vancouver has pushed many illicit drug users into peripheral urban areas, reducing their access to specialized social support and clinical services (60, 212). It may also be explained by a shift in the types of illicit drugs being consumed in this setting. A massive increase has been observed
in the use of crack cocaine (213) and crystal methamphetamine (214) among IDU between 1996 and the mid 2000s, which are stimulants that have been correlated with malnutrition and hunger in other studies (215, 216). Individuals reporting current use of cocaine, heroine, speedball, and/or crystal methamphetamine were almost twice as likely to be food insecure, when adjusting for other covariates. This finding is consistent with other studies that have found illicit drug use is associated with increased odds of food insecurity (56, 125), and are partially explained by the fact that drug addiction modifies eating habits (217, 218) and leads individuals to prioritize drugs over food intake (68, 217). Further studies should aim to assess specific structural and behavioural factors that place illicit drug users at greater risk of food insecurity, and that may be mitigated by harm reduction and social support services.

Individuals reporting symptoms of depression had 2.3 times increased odds of being food insecure. This finding is consistent with studies that have found a significant association between food insecurity and depression in non-HIV-infected populations (86, 89, 203, 204). Food insufficiency has been associated with poor mental health status among adults and adolescents, including symptoms of depression, dysthymia and suicide (86, 89). Conversely, depressive symptoms have been associated with insufficient food intake, and reduced consumption of quality foods, particularly among women (219, 220). The prevalence of major depressive episodes or generalized anxiety disorders may increase with food insecurity (204). The finding that symptoms of depression are associated with food insecurity is consistent with a study in San Francisco that found food insecurity among HIV-infected homeless and marginally housed individuals was strongly associated with poor mental health status (131). It also supports a study that found significant decreases in dietary macronutrient intake among HIV-infected individuals who developed depression, compared to those who did not (221). Future research is required to determine whether depression is a cause or consequence of food insecurity, to ascertain the extent to which depression aggravates food insecurity among individuals on ART, and whether these interactions differ by gender in this setting. In the
meantime, nutrition support services aimed at HIV-infected individuals in BC should explore programmatic links with mental health services.

Of note, Aboriginal ancestry was not associated with food insecurity in this sample of hard-to-reach individuals receiving ART. This finding is in contrast to data from a recent national survey which found that Aboriginal households were significantly more likely to be food insecure than non-Aboriginal households (222). Elevated prevalence of food insecurity among Aboriginals in the general population has been attributed in part to reduced access to traditional foods due to erosion of knowledge and culture, increased urban migration, restrictive government regulations and cost (223, 224). The relatively low prevalence of food insecurity among Aboriginals observed in this study sample suggests that HIV-positive Aboriginals may have benefited from targeted social support and nutritional services in Metro Vancouver and Prince George where the majority of participants were surveyed. Further research is necessary to understand the prevalence and correlates of food insecurity among HIV-positive Aboriginals in more rural and remote settings of BC.

This study has several limitations. Due to the cross-sectional design, this study cannot infer causality, or potential social, structural and biologic mechanisms that may link food insecurity to characteristics. LISA is not a random sample of HIV-positive individuals receiving ART; therefore, generalizations of analytic findings to individuals on ART throughout BC may be limited. The scale used in this analysis was abbreviated from the original Radimer/Cornell version (Appendix 2). Due to the high sensitivity of the scale, it is therefore possible the food insecurity estimate reported in this analysis is an underestimation of the true population parameter. However, the impact of this misclassification bias on observed prevalence estimates may have been cancelled out by the presence of selection bias. The modest financial incentive given to participants may have increased the probability of sampling people who are food insecure, thereby inflating prevalence estimates. Information (measurement) bias, and specifically non-differential misclassification of food insecurity status may have led food insecure participants to be equally misclassified among exposed and non-exposed groups, biasing
adjusted measures of association towards the null. Accordingly, it is possible that the strengths of association between food insecurity and explanatory variables were underestimated. Because survey data were self-reported, this study may have also been susceptible to recall bias and social desirability bias. However, there is no reason to believe that the magnitude of these biases would differ between food secure and insecure groups. This study did not use detailed measures of nutritional status. The use of nutrition-specific clinical markers and more detailed questionnaire surveys would have allowed us to identify macro or micronutrient deficiencies in our cohort, which are common among HIV-positive populations (55), and known to contribute to weight loss, opportunistic infections, disease progression, and accelerated time to death (169, 225-228). Future studies examining food insecurity among HIV-positive populations should seek to identify clinical markers of food insecurity, and more closely evaluate the social, structural and biological pathways linking food insecurity to drug use, low-income status, tobacco use, younger age and symptoms of depression.

In summary, this study suggests that food access and utilization among hard-to-reach HIV-infected individuals on ART may have decreased over the last 10 years. These findings are concerning in light of the fact that food insecurity has been associated with decreased virologic suppression, poor CD4 response and high mortality among HIV-treated individuals in resource-rich settings (23, 24). The association between food security and lower socio-economic status, younger age, illicit drug and tobacco use, and depressive symptoms suggests that a compendium of behavioural and environmental risk factors is associated with this population’s food security status. Further research is required to ascertain whether this high burden of food insecurity, and specifically hunger (as the most severe manifestation) is adversely impacting ART outcomes among specific vulnerable sub-groups. This is an important prerequisite to identifying programmatic and policy responses that aim to improve food security among HIV-infected populations.
Table 3.1 Responses to Radimer/Cornell food security measures among HIV-infected individuals receiving highly active antiretroviral therapy in British Columbia, Canada (n= 457)

<table>
<thead>
<tr>
<th>Food security measures</th>
<th>Never true n (%)</th>
<th>Often/Sometimes true n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I worry whether my food will run out before I get money to buy more</td>
<td>192 (42.0)</td>
<td>265 (58.0)</td>
</tr>
<tr>
<td>I worry about whether the food that I can afford to buy for my household will be enough</td>
<td>180 (39.4)</td>
<td>277 (60.6)</td>
</tr>
<tr>
<td>The food that I bought just didn't last, and I didn't have money to get more</td>
<td>199 (43.5)</td>
<td>258 (56.5)</td>
</tr>
<tr>
<td>I ran out of the foods that I needed to put together a meal and I didn't have money to get more</td>
<td>195 (42.7)</td>
<td>262 (57.3)</td>
</tr>
<tr>
<td>We eat the same thing for several days in a row because we only have a few different kinds of food on hand and don't have money to buy more</td>
<td>235 (51.4)</td>
<td>222 (48.6)</td>
</tr>
<tr>
<td>I am often hungry, but I don't eat because I can't afford enough food</td>
<td>289 (63.2)</td>
<td>168 (36.8)</td>
</tr>
<tr>
<td>I eat less than I think I should because I don't have enough money for food</td>
<td>257 (56.2)</td>
<td>200 (43.8)</td>
</tr>
<tr>
<td>I can't afford to eat properly</td>
<td>233 (51.0)</td>
<td>224 (49.0)</td>
</tr>
</tbody>
</table>
Table 3.2 Bivariate analysis of characteristics associated with food insecurity among HIV-infected individuals receiving highly active antiretroviral therapy in British Columbia, Canada (n= 457)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Categorization</th>
<th>Food insecure</th>
<th>Food secure</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>324 (71%)</td>
<td>133 (29%)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>93 (28.7)</td>
<td>22 (16.5)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>231 (71.3)</td>
<td>111 (83.5)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Median, IQR¹</td>
<td>45.1 (39.4, 50.2)</td>
<td>48.8 (42.7, 56.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aboriginal ancestry</td>
<td>No</td>
<td>199 (61.4)</td>
<td>108 (81.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>125 (38.6)</td>
<td>25 (18.8)</td>
<td></td>
</tr>
<tr>
<td>Sexual identity</td>
<td>Gay/lesbian/bisexual</td>
<td>88 (27.2)</td>
<td>70 (52.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Straight</td>
<td>236 (72.8)</td>
<td>63 (47.4)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td>&lt; High school</td>
<td>160 (49.4)</td>
<td>34 (25.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>≥ High school</td>
<td>164 (50.6)</td>
<td>99 (74.4)</td>
<td></td>
</tr>
<tr>
<td>Annual income</td>
<td>≥ $15,000</td>
<td>76 (23.6)</td>
<td>84 (63.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&lt; $15,000</td>
<td>246 (76.4)</td>
<td>48 (36.4)</td>
<td></td>
</tr>
<tr>
<td>DTES residency¹</td>
<td>No</td>
<td>185 (60.1)</td>
<td>104 (80.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>123 (39.9)</td>
<td>25 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Unstable housing</td>
<td>No</td>
<td>137 (42.4)</td>
<td>22 (16.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>186 (57.6)</td>
<td>111 (83.5)</td>
<td></td>
</tr>
<tr>
<td>Financial dependents</td>
<td>No</td>
<td>305 (94.1)</td>
<td>118 (88.7)</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>19 (5.9)</td>
<td>15 (11.3)</td>
<td></td>
</tr>
<tr>
<td>Illicit drug use</td>
<td>No</td>
<td>138 (42.6)</td>
<td>103 (77.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>186 (57.4)</td>
<td>30 (22.6)</td>
<td></td>
</tr>
<tr>
<td>Alcohol dependency</td>
<td>No</td>
<td>118 (37.2)</td>
<td>83 (63.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>199 (62.8)</td>
<td>48 (36.6)</td>
<td></td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>No</td>
<td>69 (21.4)</td>
<td>78 (58.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>253 (78.6)</td>
<td>55 (41.4)</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>Median, IQR¹</td>
<td>22.4 (20.4, 24.3)</td>
<td>23.9 (21.7, 26.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>In kg/m²</td>
<td>(20.4, 24.3)</td>
<td>(21.7, 26.7)</td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>No</td>
<td>108 (33.3)</td>
<td>88 (66.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>216 (66.7)</td>
<td>45 (33.8)</td>
<td></td>
</tr>
<tr>
<td>Adherence</td>
<td>&lt; 95%</td>
<td>59 (19.2)</td>
<td>11 (8.4)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>≥ 95%</td>
<td>248 (80.8)</td>
<td>120 (91.6)</td>
<td></td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>Median, IQR¹</td>
<td>310.0 (190.0, 470.0)</td>
<td>400.0 (285.0, 630.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>In cells/µl</td>
<td>(190.0, 470.0)</td>
<td>(285.0, 630.0)</td>
<td></td>
</tr>
<tr>
<td>HIV viral load</td>
<td>Median, IQR¹</td>
<td>2.3 (2.3, 2.3)</td>
<td>2.3 (2.3, 2.3)</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>In Log₁₀ copies/mL</td>
<td>(2.3, 2.3)</td>
<td>(2.3, 2.3)</td>
<td></td>
</tr>
</tbody>
</table>

1. Interquartile range
2. Vancouver Downtown Eastside residency
Table 3.3 Univariate and multivariate analyses of factors associated with food insecurity among HIV-infected individuals receiving highly active antiretroviral therapy in British Columbia, Canada (n=457)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariate OR&lt;sup&gt;1&lt;/sup&gt; (95% CI&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Multivariate AOR&lt;sup&gt;3&lt;/sup&gt; (95% CI&lt;sup&gt;2&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs. female</td>
<td>0.41 (0.22 - 0.76)</td>
<td>--</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 10 year increase</td>
<td>0.93 (0.91 - 0.96)</td>
<td>0.95 (0.92 - 0.98)</td>
</tr>
<tr>
<td>Aboriginal ancestry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>2.55 (1.51 - 4.32)</td>
<td>1.65 (0.88 - 3.10)</td>
</tr>
<tr>
<td>Sexual identity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Straight vs. gay/lesbian/bisexual</td>
<td>3.10 (1.97 - 4.86)</td>
<td>--</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ High school vs. &lt; high school</td>
<td>2.82 (1.73 - 4.59)</td>
<td>--</td>
</tr>
<tr>
<td>Annual income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$15,000 vs. ≥$15,000</td>
<td>5.52 (3.45 - 8.84)</td>
<td>3.15 (1.83 - 5.44)</td>
</tr>
<tr>
<td>DTES residency&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>2.95 (1.77 - 4.91)</td>
<td>--</td>
</tr>
<tr>
<td>Unstable housing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>0.26 (0.15 - 0.45)</td>
<td>--</td>
</tr>
<tr>
<td>Financial dependents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>0.60 (0.26 - 1.39)</td>
<td>--</td>
</tr>
<tr>
<td>Illicit drug use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>4.38 (2.68 - 7.15)</td>
<td>1.85 (1.03 - 3.33)</td>
</tr>
<tr>
<td>Alcohol dependency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>2.50 (1.60 - 3.91)</td>
<td>--</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>5.27 (3.29 - 8.46)</td>
<td>2.30 (1.30 - 4.07)</td>
</tr>
<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per one unit increase</td>
<td>0.89 (0.84 - 0.95)</td>
<td>0.94 (0.88 - 1.01)</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>3.41 (2.16 - 5.38)</td>
<td>2.34 (1.38 - 3.96)</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥95% vs. &lt;95%</td>
<td>0.41 (0.20 - 0.84)</td>
<td>--</td>
</tr>
<tr>
<td>CD4 cell count (Cells/µl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 100 cell decrease</td>
<td>0.84 (0.77 - 0.92)</td>
<td>--</td>
</tr>
<tr>
<td>HIV RNA viral load (Log&lt;sub&gt;10&lt;/sub&gt; copies/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per log&lt;sub&gt;10&lt;/sub&gt; increase</td>
<td>1.61 (1.10 - 2.36)</td>
<td>--</td>
</tr>
</tbody>
</table>

1. Odds Ratio  
2. 95% Confidence Interval  
3. Adjusted Odds Ratio  
4. Vancouver Downtown Eastside residency
CHAPTER 4: RELATIONSHIP BETWEEN HUNGER, ADHERENCE AND PLASMA HIV RNA SUPPRESSION AMONG HIV-POSITIVE ILLICIT DRUG USERS RECEIVING ART IN METROPOLITAN VANCOUVER, BC

4.1 Synopsis

**Background:** Previous studies suggest that illicit drug users face multiple individual and structural barriers to achieving optimal health and HIV treatment outcomes. However, little is known about the potential impact of food insufficiency on plasma HIV RNA load suppression among drug users receiving ART. **Methods:** The objective of this study was to examine the potential relationship between hunger and plasma HIV RNA suppression among HIV-positive illicit drug users receiving ART. A cross-sectional sample was derived from the ACCESS cohort in Metropolitan Vancouver, BC. Multivariate logistic regression was used to assess the potential relationship between hunger and plasma HIV RNA viral load suppression. Stratification was used to explore the potential modifying effect of adherence level on this relationship. **Results:** Among 406 participants, 235 (62.7%) reported ‘being hungry and unable to afford enough food’, and 241 (59.4%) had plasma HIV RNA viral load <50 copies/ml. In unadjusted analyses, self-reported hunger was associated with lower odds of plasma HIV RNA viral load suppression (OR = 0.59, 95% CI: 0.39-0.90, p = 0.015). In multivariate analyses, this association was no longer significant after controlling for socio-demographic, behavioral and clinical characteristics (AOR = 0.65, 95% CI: 0.37-1.10, p = 0.105). Adjusted models stratified by varying levels of adherence did not alter the magnitude or direction of this association. **Discussion:** Hunger was commonly reported among illicit drug users in this setting. Although there was an association between hunger and lower likelihood of plasma HIV RNA suppression, this did not persist in multivariate analyses. Further research is required to understand the relationships between adherence, food insufficiency and HIV treatment outcomes among HIV-positive illicit drug users receiving ART.
4.2 Introduction

There were an estimated 149 to 272 million illicit drug users globally in 2009, including approximately 2.8 million living with HIV (229). The universal uptake and effective use of ART among injection drug users (IDU) has been identified by the UN as a key strategy to eliminate AIDS-related deaths and HIV incidence by year 2015 (230). Adherent ART use has shown to predictably suppress plasma HIV RNA viral load to undetectable levels, resulting in reduced risk of HIV-related morbidity and mortality at the individual level, transmission between serodiscordant contacts (16-18), and decreased HIV incidence at the population level (19-21). However, illicit drug users continue to face multiple socio-structural, individual and provider-based barriers to achieving optimal HIV clinical outcomes (29, 61).

Previous studies suggest that illicit drug users are highly vulnerable to food insecurity (68, 200), a state without “physical, social and economic access to sufficient, safe and nutritious food” to meet dietary needs (3). A recent study among 1,053 HIV-negative illicit drug users in Vancouver, BC, found that 65% experienced hunger (56), considered the most severe form of food insecurity (88, 192). Illicit drug users living with HIV/AIDS may have heightened risk of insufficient caloric intake and malnutrition for social, behavioural and biologic reasons (231, 232). Food insufficiency and HIV/AIDS are interlinked in a vicious cycle (23, 24) which is magnified in persons with addiction due to drug-related alterations in appetite, metabolic functions, nutrient absorption and access to food (39, 232-234). Hunger and malnutrition among HIV-positive illicit drug users have been associated with increased behavioural risk of HIV transmission (37), suboptimal ART adherence (235), HIV-related wasting (35), and mortality (34).

Little is known about the potential relationship between food insufficiency and virologic response to ART among illicit drug users, which is essential to informing local and global HIV treatment as prevention efforts. Previous studies on this topic have been conducted in the US and have had varying results (38, 64, 69). The generalizability of findings to illicit drug users in
other settings has been limited by differences in social, structural and health care environments. This study therefore sought to examine the potential relationship between hunger and virologic suppression in a cohort of HIV-positive illicit drug users in BC. This study hypothesized that the relationship between hunger and virologic response to ART was modified by adherence.

4.3 Methods

4.3.1 Study Sample: ACCESS

Survey data for this analysis were obtained from the ACCESS cohort, and linked to clinical and laboratory data contained in the provincial HIV/AIDS DTP administrative database. Eligibility criteria for the current study sample, detailed sampling and recruitment procedures of these cohorts are described in Sections 1.8.1 and 1.8.3. Briefly, ACCESS includes HIV-positive illicit drug users aged 18 years or older and residing in the Metropolitan Vancouver area. Community-based recruitment strategies are focused in the DTES of Vancouver.

4.3.2 Variable Selection

The primary outcome variable of interest was plasma HIV RNA viral load suppression, defined as < 50 copies/mL (polymerase chain reaction) (73). Plasma HIV RNA was measured using the Roche Amplicor Monitor assay (Roche Diagnostics, Laval, Quebec, Canada), applying either the standard method or ultrasensitive adaptation. A viral load value was obtained for each participant by calculating their respective mean plasma HIV RNA viral load within the past six months, and then dichotomizing the value. If a participant had no observations in the last six months, we used the most recent observation available. Measurement was restricted to persons receiving ART at time of interview.

The primary explanatory variable of interest was food insufficiency. Food insufficiency
constitutes occasional or chronic inadequate food intake due to lack of resources and physical sensations of hunger (236, 237). For the purposes of our analysis, food insufficiency was defined as responding ‘yes’ to the question: “I am hungry, but don’t eat because I can’t afford enough food”. This definition was extracted from the Radimer/Cornell food insecurity scale (88) and has been validated for use at the individual-level in numerous North American settings (237-239).

Several secondary socio-demographic, behavioural, and clinical explanatory variables were examined and hypothesized to confound the relationship between hunger and HIV RNA viral load suppression. Socio-demographic variables included: age (per 10 year increase), gender (male vs. female), Aboriginal ancestry (yes vs. no), homelessness (no fixed address, street vs. other); educational attainment (≥ high school diploma vs. other), monthly income (≥CAD$1,050 vs. <CAD$1,050, based on median split), and money spent on drugs per day (considered a surrogate of frequency and intensity of drug use (68)) (≥CAD$60 vs. <CAD$60, based on median split), and incarceration (yes vs. no). Illicit drug use behaviors considered in the analysis included: at least daily heroin injection (yes vs. no), at least daily non-injection crack/rock (yes vs. no), at least daily injection crack/rock (yes vs. no), any injection or non-injection drug binge, defined as “[a time when you] injected drugs more than usual, or used any non-injection drugs more than usual” (yes vs. no), daily alcohol use (≥4 drinks vs. <4 drinks, based on median split). All behavioural variable definitions were identical to previous reports (72). All variables were based on a recall period of six months, unless specified otherwise. Clinical variables considered in this analysis included: symptoms of depression in the past week (≥16 CES-D score vs. <16 CES-D score) (202), year of ART initiation and plasma HIV RNA viral load (per log 10). CD4 cell counts (per 100 cells/µl) were recorded using flow cytometry and fluorescent monoclonal antibody analysis (Beckman Coulter, Inc., Mississauga, Ontario, Canada). As previously described, ART adherence was measured on the basis of prescription refill compliance (240), defined as the number of days ART was dispensed over the number of days an individual was eligible for ART, in the past 12 months (≥ 95% vs. < 95%). This variable
has shown to reliably predict virologic suppression (241-243) and survival (72, 240) among illicit drug users.

4.3.3 Statistical Analyses

Univariate statistics were used to determine factors associated with self-reported hunger. Categorical explanatory variables were analyzed using Pearson’s Chi-Square test, and continuous variables were analyzed using the Wald test. To estimate the independent effect of hunger on plasma HIV RNA viral load suppression, a multivariate model was constructed using an adaptation of a method described previously by Greenland and colleagues (244, 245). This manual backward stepwise approach involved first fitting a full model, including all explanatory variables, and noting the value of the coefficient associated with self-reported hunger. Reduced models were then constructed, each removing one secondary explanatory variable from the full set of secondary explanatory variables. Comparing the value of the coefficient for hunger in the full model and each of the reduced models, secondary variables were removed corresponding to the smallest relative change in the coefficient for hunger. This iterative process continued until the maximum change of the value for hunger from the full model exceeded 5%. The intent of this model building strategy was to retain secondary variables in the final multivariate model with greater relative influence on the relationship between hunger and plasma HIV RNA viral load suppression. This technique has been previously applied in HIV-positive studies to estimate the independent relationship between a hypothesized predictor variable and clinical outcome (246, 247).

In order to examine potential non-behavioural (i.e. nutritional or mental health) mechanisms (24) in the relationship between hunger and plasma HIV RNA viral load suppression, additional multivariate models were built controlling for 95% adherence as a potential confounder. To test whether the relationship between hunger and plasma HIV RNA suppression was modified by differences in ART adherence level, which is considered a key
behavioural mechanism (24), multivariate models were re-run stratified by >95% vs. ≤95% adherence. Given the overlapping constructs implicit in several of the secondary explanatory variables under investigation, variance inflation factor (VIF) values were calculated to assess possible multicollinearity among variables in all final models. All statistical analyses were completed using R v2.10.1 (R Foundation, Vienna, Austria).

### 4.4 Results

A total of 406 participants were eligible for the present analysis. Overall, the median age within the sample was 44.4 years [IQR: 38.9 - 48.8 years]; 134 (33.0%) were female; and 158 (38.9%) self-identified as being of Aboriginal ancestry. A total of 235 (62.7%) reported being hungry and unable to afford enough food, and 165 (40.6%) had plasma HIV RNA viral load <50 copies/ml at time of interview.

Socio-demographic, behavioural and clinical characteristics associated with self-reported hunger in univariate analyses are shown in Table 4.1. Unadjusted factors associated with self-reported hunger among illicit drug users included: younger age (OR = 0.75, 95% CI: 0.56 - 0.99, \( p = 0.045 \)); homelessness (OR = 2.89, 95% CI: 1.24 - 6.75, \( p = 0.014 \)); spending ≥$60/day on drugs (OR = 2.23, 95% CI: 1.43 - 3.48, \( p < 0.001 \)); incarceration (OR = 1.71, 95% CI: 1.04 - 2.82, \( p < 0.035 \)); symptoms of depression (OR = 3.54, 95% CI: 2.26 - 5.55, \( p < 0.001 \)).

Univariate analysis of factors associated with plasma HIV RNA suppression among study participants are presented in Table 4.2. As shown, self-reported hunger was inversely associated with plasma HIV RNA suppression (OR = 0.59, 95% CI: 0.38 - 0.90, \( p = 0.015 \)). Other factors associated with plasma HIV RNA suppression in unadjusted analyses included: older age (OR = 2.19, 95% CI: 1.64 - 2.93, \( p < 0.001 \)); male gender (OR = 1.81, 95% CI: 1.17 - 2.80, \( p = 0.008 \)); Aboriginal ancestry (OR = 0.61, 95% CI: 0.41 - 0.93, \( p = 0.021 \)); homelessness (OR = 0.32, 95% CI: 0.14 - 0.712, \( p = 0.005 \)); spending ≥$60/day on drugs (OR = 0.58, 95% CI: 0.38 - 0.90, \( p = 0.015 \)).
Multivariate analyses of factors associated with plasma HIV RNA suppression among illicit drug users receiving ART are presented in Table 4.3. Hunger was no longer significantly associated with virologic non-suppression after controlling for age, homelessness, daily expenditure on drugs, monthly income, and 95% adherence (Model 1) (AOR = 0.64, 95% CI: 0.37 – 1.10, p = 0.105). The association between hunger and virologic non-suppression was also not significant in the model that excluded adherence, and controlled for age, gender, homelessness, education, daily expenditure on drugs, monthly income, symptoms of depression, binge drug use and CD4 cell count (Model 2) (AOR = 0.77, 95% CI: 0.44 - 1.33, p = 0.349). VIF values for all secondary explanatory variables were <6.50, indicating no concerns with multicollinearity in final models.

In analyses stratified by adherence (Table 4.4), among participants with ≥95% adherence, hunger was associated with 39% reduced odds of plasma HIV RNA suppression (Model 3) (AOR: 0.61, 95% CI: 0.23 - 1.58, p = 0.307). Conversely, among individuals with <95% adherence, hunger was associated with 46% lower odds of plasma HIV RNA suppression (Model 4) (AOR: 0.56, 95% CI: 0.26 - 1.22, p = 0.144). Neither of these associations was found to be statistically significant.

4.5 Discussion

This study aimed to explore the relationship between hunger and virologic suppression among illicit drug users receiving ART in Vancouver, BC. Over two-thirds of participants reported hunger in this sample, double that observed among HIV-positive individuals in diverse North American settings (38, 64, 248). Over half of illicit drug users in this setting had suppressed viral loads. While hunger was inversely associated with this outcome in univariate analysis, the strength of association weakened after controlling for socio-demographic,
behavioural and clinical characteristics, suggesting these variables had a positive statistical confounding effect. Varying levels of adherence did not alter the magnitude or direction of this association, indicating that multiplicative interaction was not present.

This study was the first to evaluate the potential impact of food insufficiency on virologic outcomes in a setting with access to universal health care and free ART, independent of the potential confounding effect of financial barriers. The direction of association observed in this analysis is consistent with results from studies in the US that have found inverse associations between food insecurity and virologic suppression (167, 235, 249). For example, in a large multisite study including 2,353 HIV-infected individuals, food insecurity was independently associated with 37% increased odds of virologic non-suppression (167). In a study among 104 homeless and marginally housed individuals receiving ART in San Francisco, severe food insecurity was independently associated with 77% decreased odds of virologic suppression (69). Findings from the current analysis differ in that the association between hunger and virologic suppression among illicit drug users was not statistically significant. This difference may be explained by variations between Canadian and US structural health care environments. Fully subsidized HIV treatment and support in BC may have had a protective effect on the relationship between hunger and virologic suppression among drug users in this setting. Alternatively, the sample may have been underpowered to detect a true association. The notion that the sample may have been insufficiently powered is supported by the fact that the prevalence of hunger was high (i.e. there was limited variability in the predictor variable); the study design was cross-sectional; and that drug use in this sample may be a bigger driver of poor virologic outcomes than food insecurity. This interpretation of results is further supported by the observation that OR point estimates remained similar across all unadjusted and adjusted analyses, despite slight fluctuations in the 95% CI.

In multivariate analyses stratified by 95% adherence (Table 4.4, Models 3 and 4), variations in adherence level did not alter the direction or magnitude of the association between hunger and plasma HIV RNA viral load suppression, suggesting that adherence was not a
significant effect modifier in this relationship. The presence of an independent marginally significant association between hunger and virologic non-suppression in analyses controlling for adherence (Table 4.3, Model 1) suggests that non-behavioural factors may have been partially mediating the relationship under study. Assuming that hunger is a reliable surrogate for insufficient food consumption, hunger may have led to poor virologic response through the following nutritional and mental health (24) mechanisms: First, observance of dietary guidelines has been described as essential for controlling HIV replication (161), and numerous PI-based regimens require consumption with food to maximize bioavailability (162). Hunger may have contributed to poor virologic response among individuals receiving PI-based regimens by impeding the pharmacokinetic effectiveness of their ARVs. Second, chronic hunger may have led illicit drug users to develop micronutrient deficiencies (30, 250), which in turn caused the HIV RNA virus to become more virulent (251) reducing ART’s ability to effectively suppress replication. The plausibility of this latter mechanism is supported by double-blind randomized controlled trials that have found a causal association between selenium (252) and multivitamin supplementation (253) and decreased plasma HIV RNA viral load. Third, hunger may have affected virologic non-suppression through mental health pathways (24). Food insufficiency has been associated with higher odds of depression in general HIV-positive groups (254) and among HIV-positive illicit drug users (130). This potential pathway has been supported by longitudinal studies that have found anti-depression medication use is associated with improved odds of virologic suppression (255). Longitudinal studies are needed to further explore the potential modulating effects of nutritional and mental health status on the relationship between food insufficiency and virologic response to ART.

The marginal association between hunger and plasma HIV RNA viral load non-suppression in Model 1 may also be explained by the presence of residual confounding, which may have resulted because: categories of hypothesized confounders were too broad (e.g. dichotomization of continuous alcohol use, income and expenditure variables, based on median split) (256, 257); variables used for adjustment were imperfect surrogates of a characteristic of
interest (e.g. daily expenditure on drugs as a surrogate of chronic, intensive drug use); confounding variables were misclassified due to inaccurate measurement tools or responder bias; or unobserved and unknown confounders were not accounted for (258). Formal statistical methods for testing the construct validity of surrogates (259) and for correcting potential confounder misclassification (260) were outside the scope of this study. However, misclassification of confounders was minimized through the use of epidemiologically validated scales, objective clinical measures, and extensive training of community-based interviewers.

The limited food access and utilization found in this population support the need to pilot and evaluate interventions to address the nutritional needs of HIV-positive illicit drug users. The high prevalence of hunger in this sample suggests that illicit drug users in this setting are living within a heightened risk environment, where socio-economic, physical and policy factors may be ‘interplaying’ (42, 43), to make them vulnerable to insufficient food access and utilization. Structural interventions, including nutritional counseling and food support, should be integrated into harm reduction strategies for this population in order to prevent HIV- and drug-related harms. Given the competing demands of food and drug use experienced by many illicit drug users in this setting (68), provision of, or referral to, nutritional counseling and nutrient support could be integrated into HIV care, treatment and harm reduction programs including syringe distribution, substitution therapy, mobile outreach services, and housing models. Food support and nutrition interventions for HIV-positive illicit drug users should be coupled with scientific evaluation in order to identify the most effective programs and policies for this vulnerable group. This operational research should consider the use of robust study design, adequate sample size, validated food security and nutrition instruments (261), and harmonized composite HIV endpoints (262) to foster generalizability and comparability of findings.

Due to uncertainty regarding the statistical power of this study sample, this study cannot make a firm conclusion regarding whether hunger among illicit drug users receiving ART is a direct impediment to achieving the individual and public health goals for HIV treatment as prevention in the province of BC. Previous studies in this context have demonstrated that illicit
drug users can significantly benefit from ART in terms of reduced disease progression (243) and improved survival (72), despite individual and environmental barriers to ART optimization. The expansion of ART access to people living with HIV/AIDS in BC, including a substantial proportion of illicit drug users, has been associated with annual decreases in community-viral load and in HIV diagnoses (263). Reduced community-viral load among illicit drug users have in turn been independently associated with decreased HIV incidence, after controlling for risky sex, syringe borrowing, and other risk factors for HIV transmission (66, 264). Low rates of adherence to ART, however, remain an important concern among illicit drug users in this setting (243, 265). Future studies are needed to understand the potential role of food insecurity in ART adherence among illicit drug users. In the meantime, addressing known social and structural barriers to ART adherence among illicit drug users in this setting, including incarceration (266), homelessness (246), and gender-related factors (267) remains of paramount importance.

This study has several limitations that warrant attention. Study sample participants were not randomly selected; therefore findings may not be representative of the general HIV-positive illicit drug users population in BC. The cross-sectional design of this study limits any ability to infer causation. The provision of participant honoraria may have introduced selection bias, increasing the probability of sampling individuals who are hungry, thus potentially inflating prevalence estimates. Information bias, and specifically responder bias, may have led to non-differential misclassification of hunger status, biasing OR estimates towards the null. Self-reported nutritional estimates have shown to be less reliable than clinical nutrition markers. For example, study participants have shown to under-report energy intake and weight, over-report height (268), and provide varying responses by gender and beliefs of social desirability (268). While the measurement tool we used to assess hunger has been extensively validated in several North American contexts (38, 64, 248), future studies could be strengthened by applying dietary intake assessment methods that have been validated for use specifically among HIV-positive illicit drug users (269, 270). Analytic techniques may have inadvertently introduced a bias due to incorrect selection of potential confounder variables (271). This challenge has been
previously highlighted in HIV (272) and nutrition (273) studies. However, a repeat multivariate analysis, including variables selected using directed acyclic graph methodology (274) generated almost identical results, suggesting this bias was not a significant concern in this study (Appendix 3).

In summary, this study examined the relationship between hunger and plasma HIV RNA suppression in a cohort of HIV-positive illicit drug users receiving ART in Metropolitan Vancouver. It observed high prevalence of hunger and failure to achieve plasma HIV RNA viral load suppression. While hunger was associated with decreased odds plasma of HIV RNA suppression in univariate analysis, this association was no longer significant after controlling for potential confounders. The persistence of marginal inverse association between hunger and virologic suppression in multivariate and stratified analyses suggests a need to further examine this relationship in larger or pooled samples of HIV-positive illicit drug users. Given the complex risk environment experienced by illicit drug users in this setting, public health efforts should consider further evaluation of the possible role of nutritional supplementation within existing harm reduction and HIV strategies and conduct further research to ascertain whether hunger in this population poses an impediment to achieving the individual and populations goals of HIV treatment as prevention.
Table 4.1 Univariate analysis of factors associated with self-reported hunger among HIV-positive illicit drug users receiving antiretroviral therapy in Vancouver, BC (n = 375)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hunger 235 (62.7%)</th>
<th>No hunger 140 (37.3%)</th>
<th>Odds Ratio (95% CI)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, interquartile range [IQR]</td>
<td>43.5 (38.7-48.0)</td>
<td>45.2 (39.6-49.9)</td>
<td>0.75 (0.56 - 0.99)</td>
<td>0.045</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>159 (67.7%)</td>
<td>97 (69.3%)</td>
<td>0.93 (0.59 - 1.46)</td>
<td>0.744</td>
</tr>
<tr>
<td>Female</td>
<td>76 (32.3%)</td>
<td>43 (30.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aboriginal ancestry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>94 (40.0%)</td>
<td>50 (35.7%)</td>
<td>1.20 (0.78 - 1.85)</td>
<td>0.409</td>
</tr>
<tr>
<td>No</td>
<td>141 (60.0%)</td>
<td>90 (64.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homelessness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>31 (13.2%)</td>
<td>7 (5.0%)</td>
<td>2.89 (1.24 - 6.75)</td>
<td>0.014</td>
</tr>
<tr>
<td>No</td>
<td>204 (86.8%)</td>
<td>133 (95.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or greater</td>
<td>205 (91.9%)</td>
<td>126 (93.3%)</td>
<td>0.81 (0.36 - 1.87)</td>
<td>0.626</td>
</tr>
<tr>
<td>Other</td>
<td>18 (8.1%)</td>
<td>9 (6.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly income</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ $1,050</td>
<td>110 (50.0%)</td>
<td>75 (57.7%)</td>
<td>0.73 (0.47 - 1.14)</td>
<td>0.164</td>
</tr>
<tr>
<td>&lt; $1,050</td>
<td>110 (50.0%)</td>
<td>55 (42.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Money spent on drugs per day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ $60</td>
<td>138 (62.7%)</td>
<td>55 (43.0%)</td>
<td>2.23 (1.43 - 3.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt; $60</td>
<td>82 (37.3%)</td>
<td>73 (57.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incarceration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>193 (82.1%)</td>
<td>102 (72.9%)</td>
<td>1.71 (1.04 - 2.82)</td>
<td>0.035</td>
</tr>
<tr>
<td>No</td>
<td>42 (17.9%)</td>
<td>38 (27.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms of depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>176 (76.2%)</td>
<td>66 (47.5%)</td>
<td>3.54 (2.26 - 5.55)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>55 (23.8%)</td>
<td>73 (52.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily injection heroin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (11.9%)</td>
<td>12 (8.6%)</td>
<td>1.44 (0.71 - 2.94)</td>
<td>0.312</td>
</tr>
<tr>
<td>No</td>
<td>207 (88.1%)</td>
<td>128 (91.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily non-injection crack</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37 (15.7%)</td>
<td>17 (12.1%)</td>
<td>1.35 (0.73 - 2.51)</td>
<td>0.338</td>
</tr>
<tr>
<td>No</td>
<td>198 (84.3%)</td>
<td>123 (87.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily injection cocaine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21 (8.9%)</td>
<td>13 (9.3%)</td>
<td>0.96 (0.46 - 1.98)</td>
<td>0.909</td>
</tr>
<tr>
<td>No</td>
<td>214 (91.1%)</td>
<td>127 (90.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any drug binge</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>104 (44.3%)</td>
<td>52 (37.1%)</td>
<td>1.34 (0.88 - 2.06)</td>
<td>0.177</td>
</tr>
<tr>
<td>No</td>
<td>131 (55.7%)</td>
<td>88 (62.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily alcohol use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 4 drinks</td>
<td>58 (24.7%)</td>
<td>33 (23.6%)</td>
<td>1.06 (0.65 - 1.74)</td>
<td>0.809</td>
</tr>
<tr>
<td>&lt; 4 drinks</td>
<td>177 (75.3%)</td>
<td>107 (76.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence to ART</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 95%</td>
<td>79 (33.6%)</td>
<td>52 (37.1%)</td>
<td>0.86 (0.55 - 1.33)</td>
<td>0.489</td>
</tr>
<tr>
<td>&lt; 95%</td>
<td>156 (66.4%)</td>
<td>88 (62.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count (per 100cell increase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, IQR</td>
<td>2.66 (1.59 - 4.14)</td>
<td>3.10 (2.01 - 4.63)</td>
<td>0.93 (0.83 - 1.04)</td>
<td>0.190</td>
</tr>
<tr>
<td>Plasma HIV RNA (per Log_{10} increase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, IQR</td>
<td>2.73 (1.65 – 4.42)</td>
<td>1.83 (1.65 – 4.39)</td>
<td>1.10 (0.95 - 1.28)</td>
<td>0.198</td>
</tr>
</tbody>
</table>

1. 95% Confidence Interval
2. Based on median split
3. Within last six months of interview
4. Within last week of interview
5. Within last 12 months of interview
Table 4.2 Univariate analysis of factors associated with plasma HIV RNA suppression among HIV-positive illicit drug users receiving antiretroviral therapy in Vancouver, BC (n = 406)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Plasma HIV RNA ≤50 copies/mL</th>
<th>Plasma HIV RNA &gt;50 copies/mL</th>
<th>Odds Ratio (95% CI)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunger</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84 (55.3%)</td>
<td>151 (67.7%)</td>
<td>0.59 (0.39 - 0.90)</td>
<td>0.015</td>
</tr>
<tr>
<td>No</td>
<td>68 (44.7%)</td>
<td>72 (32.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, interquartile range [IQR]</td>
<td>46.7 (41.5 - 51.7)</td>
<td>42.4 (37.0 - 47.0)</td>
<td>2.19 (1.64 - 2.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>123 (74.5%)</td>
<td>149 (61.8%)</td>
<td>1.81 (1.17 - 2.80)</td>
<td>0.008</td>
</tr>
<tr>
<td>Female</td>
<td>42 (25.5%)</td>
<td>92 (38.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aboriginal ancestry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>53 (32.1%)</td>
<td>105 (43.6%)</td>
<td>0.61 (0.41 - 0.93)</td>
<td>0.021</td>
</tr>
<tr>
<td>No</td>
<td>112 (67.9%)</td>
<td>136 (56.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homelessness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (4.9%)</td>
<td>33 (13.7%)</td>
<td>0.32 (0.14 - 0.72)</td>
<td>0.005</td>
</tr>
<tr>
<td>No</td>
<td>157 (95.1%)</td>
<td>208 (86.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ High school</td>
<td>145 (93.6%)</td>
<td>210 (91.7%)</td>
<td>1.31 (0.59 - 2.90)</td>
<td>0.503</td>
</tr>
<tr>
<td>Other</td>
<td>10 (6.4%)</td>
<td>19 (8.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly income £1,050</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ $1,050</td>
<td>83 (54.6%)</td>
<td>117 (51.5%)</td>
<td>1.13 (0.75 - 1.71)</td>
<td>0.558</td>
</tr>
<tr>
<td>&lt; $1,050</td>
<td>69 (45.4%)</td>
<td>110 (48.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Money spent on drugs per day £60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ $60</td>
<td>76 (48.4%)</td>
<td>136 (61.8%)</td>
<td>0.58 (0.38 - 0.88)</td>
<td>0.010</td>
</tr>
<tr>
<td>&lt; $60</td>
<td>81 (51.6%)</td>
<td>84 (38.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incarceration £3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>130 (78.8%)</td>
<td>187 (77.6%)</td>
<td>1.07 (0.66 - 1.73)</td>
<td>0.775</td>
</tr>
<tr>
<td>No</td>
<td>35 (21.2%)</td>
<td>54 (22.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms of depression £4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>96 (61.9%)</td>
<td>152 (67.9%)</td>
<td>0.77 (0.50 - 1.18)</td>
<td>0.234</td>
</tr>
<tr>
<td>No</td>
<td>59 (38.1%)</td>
<td>72 (32.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily injection heroin £3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (8.5%)</td>
<td>32 (13.3%)</td>
<td>0.61 (0.31 - 1.17)</td>
<td>0.138</td>
</tr>
<tr>
<td>No</td>
<td>151 (91.5%)</td>
<td>209 (86.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily non-injection crack £3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (13.3%)</td>
<td>36 (14.9%)</td>
<td>0.88 (0.50 - 1.55)</td>
<td>0.650</td>
</tr>
<tr>
<td>No</td>
<td>43 (86.7%)</td>
<td>205 (85.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily injection cocaine £3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (12.1%)</td>
<td>17 (7.1%)</td>
<td>1.82 (0.92 - 3.59)</td>
<td>0.085</td>
</tr>
<tr>
<td>No</td>
<td>145 (87.9%)</td>
<td>224 (92.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any drug binge £3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>67 (40.6%)</td>
<td>105 (43.6%)</td>
<td>0.89 (0.59 - 1.32)</td>
<td>0.553</td>
</tr>
<tr>
<td>No</td>
<td>98 (59.4%)</td>
<td>136 (56.4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily alcohol use £2,3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 4 drinks</td>
<td>44 (26.7%)</td>
<td>61 (25.3%)</td>
<td>1.07 (0.68 - 1.69)</td>
<td>0.759</td>
</tr>
<tr>
<td>&lt; 4 drinks</td>
<td>121 (73.3%)</td>
<td>180 (74.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence to ART £5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 95%</td>
<td>105 (63.6%)</td>
<td>38 (15.8%)</td>
<td>9.35 (5.85 - 14.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt; 95%</td>
<td>60 (36.4%)</td>
<td>203 (84.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count (per 100cell increase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, IQR</td>
<td>3.80 (2.48 - 4.90)</td>
<td>2.41 (1.25 - 3.55)</td>
<td>1.56 (1.38 - 1.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ART initiation (per year increase)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, IQR</td>
<td>2000 (1997 - 2003)</td>
<td>1999 (1997 - 2004)</td>
<td>0.99 (0.95 – 1.04)</td>
<td>0.821</td>
</tr>
</tbody>
</table>

1. 95% Confidence Interval
2. Based on median split
3. Within last six months of interview
4. Within last week of interview
5. Within last 12 months of interview
Table 4.3 Multivariate analysis of factors associated with plasma HIV RNA suppression among HIV-positive illicit drug users receiving antiretroviral therapy in Vancouver, BC (n = 406)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plasma HIV RNA ≤50 copies/mL (Model 1: incl. 95% adherence)</th>
<th>Plasma HIV RNA ≤50 copies/mL (Model 2: excl. 95% adherence)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AOR 1 95% CI 2 p - value</td>
<td>AOR 1 95% CI 2 p - value</td>
</tr>
<tr>
<td>Self-reported hunger</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>0.64 (0.37 – 1.10) 0.105</td>
<td>0.77 (0.44 – 1.33) 0.349</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 10 year increase</td>
<td>1.65 (1.13 – 2.41) 0.010</td>
<td>1.81 (1.22 – 2.69) 0.003</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs. female</td>
<td>--</td>
<td>1.39 (0.78 – 2.47) 0.269</td>
</tr>
<tr>
<td>Homelessness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>0.39 (0.15 – 1.02) 0.055</td>
<td>0.49 (0.19 – 1.28) 0.148</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ High school vs. other</td>
<td>--</td>
<td>1.68 (0.57 – 5.00) 0.348</td>
</tr>
<tr>
<td>Monthly income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥$1,050 vs. &lt;$1,050</td>
<td>0.72 (0.42 – 1.21) 0.216</td>
<td>0.74 (0.44 – 1.25) 0.263</td>
</tr>
<tr>
<td>Average spent on drugs per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥$60 vs. &lt;$60</td>
<td>0.82 (0.49 – 1.39) 0.467</td>
<td>0.72 (0.43 – 1.23) 0.232</td>
</tr>
<tr>
<td>Symptoms of depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>--</td>
<td>1.15 (0.65 – 2.04) 0.627</td>
</tr>
<tr>
<td>Any drug binge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>--</td>
<td>1.60 (0.45 – 1.28) 0.303</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 100 increase</td>
<td>--</td>
<td>1.54 (1.32 – 1.80) &lt;0.001</td>
</tr>
<tr>
<td>Adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥95% vs. &lt;95%</td>
<td>7.30 (4.26 – 12.49) &lt;0.001</td>
<td>--</td>
</tr>
</tbody>
</table>

1. Adjusted Odds Ratio
2. 95% Confidence Interval
3. Based on median split
4. Within last week of interview
5. Within last six months of interview
6. Within last 12 months of interview
Table 4.4 Multivariate analysis of factors associated with HIV RNA viral load suppression, stratified by adherence level, among HIV-positive illicit drug users receiving antiretroviral therapy in Vancouver, BC (n = 406)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Plasma HIV RNA ≤50 copies/mL (Model 3: with &lt;95% adherence)</th>
<th>Plasma HIV RNA ≤50 copies/mL (Model 4: with ≥95% adherence)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AOR 2 95% CI 3 p – value</td>
<td>AOR 2 95% CI 3 p – value</td>
</tr>
<tr>
<td>Self-reported hunger</td>
<td>0.56 (0.26 - 1.22) 0.144</td>
<td>0.61 (0.23 - 1.58) 0.307</td>
</tr>
<tr>
<td>Aboriginal ancestry</td>
<td>--</td>
<td>0.69 (0.27 - 1.73) 0.424</td>
</tr>
<tr>
<td>Homelessness</td>
<td>0.51 (0.13 - 1.98) 0.333</td>
<td>--</td>
</tr>
<tr>
<td>Education</td>
<td>1.54 (0.30 - 7.92) 0.605</td>
<td>--</td>
</tr>
<tr>
<td>Monthly income 4</td>
<td>0.87 (0.41 - 1.84) 0.717</td>
<td>0.59 (0.24 - 1.45) 0.247</td>
</tr>
<tr>
<td>Average spent on drugs per day 4</td>
<td>0.85 (0.40 - 1.84) 0.68</td>
<td>0.59 (0.25 - 1.39) 0.230</td>
</tr>
<tr>
<td>Symptoms of depression</td>
<td>--</td>
<td>1.44 (0.52 - 3.98) 0.479</td>
</tr>
<tr>
<td>Daily non-injection crack 6</td>
<td>--</td>
<td>3.19 (0.58 - 17.70) 0.184</td>
</tr>
<tr>
<td>Daily injection cocaine 6</td>
<td>--</td>
<td>2.01 (0.39 - 10.43) 0.404</td>
</tr>
<tr>
<td>Any drug binge 6</td>
<td>--</td>
<td>0.60 (0.25 - 1.40) 0.235</td>
</tr>
<tr>
<td>Daily alcohol use 5,6</td>
<td>--</td>
<td>0.59 (0.22 - 1.56) 0.289</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>1.63 (1.30 - 2.04) &lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td>Year of ART initiation</td>
<td>1.05 (0.96 - 1.14) 0.316</td>
<td>--</td>
</tr>
</tbody>
</table>

1. Within last 12 months of interview
2. Adjusted Odds Ratio
3. 95% Confidence Interval
4. Based on median split
5. Within last week of interview
6. Within last six months of interview
CHAPTER 5: RELATIONSHIP BETWEEN FOOD INSECURITY AND MORTALITY AMONG HIV-POSITIVE INJECTION DRUG USERS RECEIVING ART IN BC, CANADA

5.1 Synopsis

**Background:** Food insecurity has been associated with an increased risk of mortality among HIV-positive individuals receiving ART in BC. To our knowledge, no studies have assessed this relationship among illicit drug users, a group particularly vulnerable to food insecurity and hunger. **Methods:** This study aimed to examine the potential relationship between food insecurity and mortality among HIV-positive IDU initiating ART across BC. Participants were recruited into the province-wide HIV/AIDS DTP in June 1998 and followed until September 2011. Cox proportional hazard models were used to ascertain associations between food insecurity/hunger and all-cause mortality, while controlling for potential confounders. **Results:** Among a total of 254 IDU, 181 (71.3%) were categorized as food insecure; 108 (42.5%) were hungry; and 7 (3.1%) had low BMI. After a median follow-up time of 13.3 years, a total of 105 (41.3%) participants died. In univariate analysis, food insecurity (hazard ratio [HR] = 2.41, 95% CI: 1.45 – 4.01) and hunger were (HR = 1.78, 95% CI: 1.21 – 2.61) associated with increased risk of mortality. In multivariate analysis, food insecurity remained significantly associated with mortality (adjusted hazard ratio [AHR] = 1.95, 95% CI: 1.07 – 3.53), and hunger was no longer significant (AHR = 1.05, 95% CI: 0.65 – 1.70). **Discussion:** These results suggest that aspects of food insecurity, other than insufficient food consumption, are placing IDU at increased risk of mortality. These findings suggest an urgent need to rigorously investigate sub-types of food insecurity driving this association, and to
strengthen social and structural supports within harm reduction and HIV treatment programs to prevent excess mortality.

5.2 Introduction

Despite the tremendous benefits of ART use on HIV disease progression and survival (13, 275), micro- and macronutrient malnutrition remain strong independent predictors of mortality among HIV-positive individuals in both high and low resource settings (164, 168, 276-284). A growing body of evidence suggests that social determinants, such as poor socio-economic status, may also adversely impact survival among people living with HIV/AIDS (285, 286). Recent studies among people living with HIV/AIDS in Canada and the US found that food insecurity is associated with increased risk of mortality (65, 286). These findings suggest that some risk groups, disproportionately burdened by food insecurity and hunger, may have heightened risk of mortality, which would warrant prioritization by public health programs and policies.

Illicit drug use is a well-known risk factor of food insecurity and poor nutritional status. Drug addiction alters dietary consumption patterns, leading individuals to eat fewer meals (287), and to often skip meals for an entire day (35). Competing demands for resources can lead illicit drug users to purchase drugs, even when they are hungry (68), and to rely on food distribution services for subsistence (288). Studies have found that illicit drug users tend to consume diets that are calorically insufficient and poor in quality (287), resulting in diverse micro- and macronutrient deficiencies (31, 35, 36, 215, 289). Studies in urban HIV-positive populations receiving HIV treatment, including a high proportion of illicit drug users, have found that food insecurity and insufficiency are
associated with HIV-related wasting (35), virologic non-suppression (64, 69) and poor immunologic response to ART (56, 64, 125).

Among hard-to-reach individuals receiving ART within the BC-wide LISA Cohort, illicit drug users were almost twice as likely to report food insecurity, compared to non-users (Chapter 3), and 64% of HIV-positive illicit drug users receiving ART in the Vancouver-based ACCESS cohort reported hunger (Chapter 4). However, to our knowledge no studies have examined whether heightened food insecurity and insufficiency in this population increases their vulnerability to excess death. This study therefore aimed to examine the potential relationship between food security, hunger and all-cause mortality among HIV-positive injection drug users (IDU) initiating ART across BC. In light of previous findings regarding the relationship between food insecurity and mortality in the general HIV-population in this setting (65), and theorized nutritional mechanisms linking these (24), this study hypothesized that food insecurity and hunger were independently associated with all-cause mortality, and that these relationships were modified by the presence of clinical undernutrition, or low BMI.

5.3 Methods

5.3.1 Study Sample: DTP

Survey data for this analysis were obtained from the provincial HIV/AIDS DTP administrative database. Detailed sampling and recruitment procedures of these cohorts are described in Sections 1.8.3. The analytic sample was restricted to DTP participants who reported ever being an IDU (either by physician or self-report) and who responded to the food security and sufficiency questions contained in the baseline enrollment survey.
5.3.2 Variable Selection

The primary outcome variable of interest was all-cause mortality. This outcome includes individuals who died due to HIV-related and other health-related causes, as well as due to injuries, accidents, trauma, assaults, drug overdose and suicide. Mortality data was collected on an ongoing basis through physician reports. This data was confirmed through electronic linkage to the British Columbia Division of Vital Statistics registry, which has been shown to capture upwards of 96% of all deaths in the province (290). Event-free participants, and individuals lost to follow-up, were right-censored on Sept 30, 2011. Statistical analyses assumed censored observations were ‘noninformative’, which is a valid assumption in light of the limited loss to follow-up in this cohort.

The primary explanatory variables of interest were food insecurity and insufficiency. Food insecurity was measured at the household and individual (adult) level using an abbreviated version of the Radimer/Cornell scale (88, 190). As recommended by Kendall et al. (190), individuals were categorized as food insecure if they gave a minimum of one positive answer (often/sometimes) to any one of the eight items measuring household or individual (adult) food insecurity. The Radimer/Cornell scale covers topics such as insufficient food intake, the physical sensation of hunger, problems with household food supply, diet quality, anxiety related to food insecurity, and efforts made to maintain household food supplies (88, 190). It has shown to be a valid measure of food insecurity and hunger on the basis of several criteria (191). Food insufficiency results from occasional or chronic inadequate food intake due to lack of resources, and includes physical sensations of hunger (236, 237). For the purposes of our analysis, food insufficiency was defined as responding ‘yes’ to the question: “I am hungry, but don’t eat because I can’t afford enough food”. This definition was extracted from the Radimer/Cornell food insecurity scale (88). The overall food insecurity scale
and individual hunger question have been validated for use at the individual and population level in numerous North American settings (237-239) (Appendix 2). These measures were collected at baseline in 1998 / 1999, as part of an enrollment survey for individuals newly initiating ART.

Underweight nutritional status was assessed as a possible effect modifier in the relationship between hunger and mortality. Weight and height measures were obtain by physician and self-reports at baseline in 1998 / 1999. Nutritional status was measured as BMI (kg/m²) value, calculated using the formula: weight/(height)². Cut-offs for underweight status were based on current WHO standards for HIV-positive individuals, defined as <18.5 kg/m² (underweight) vs ≥18.5 kg/m² (not underweight) (291). BMI measures reflect lean body mass and fat mass. Measures of body weight loss, based on BMI, have shown to detect malnutrition at an earlier stage than other anthropometric measures, and is considered a sensitive screening tool for malnutrition among people living with HIV/AIDS (292).

Secondary explanatory variables hypothesized to confound the relationship between food insecurity, hunger and mortality were based on findings from previous literature, and were consistent with a previous study examining the impacts of food insecurity on mortality among HIV-positive individuals in this setting (65). Socio-demographic variables included: age at ARV start date (continuous); gender (male vs. female); Aboriginal ancestry (yes vs. no); annual income (>CAD$1,500 vs. ≤CAD$1,500), with a dichotomous split based on low income cut-off (293); education (>high school vs. ≤high school graduation); and unstable housing (yes vs. no), defined as living in a hotel, boarding house, group home, jail, in the street, or having no fixed address at the time of the survey. Clinical variables considered in this analysis included: ART use (yes vs. no); PI-based regimen (yes vs. no); and AIDS diagnosis (yes vs. no), defined according to CDC classification (294); plasma HIV RNA viral load (per log₁₀
copies/mL), measured at most recent date prior to survey; CD4 cell counts (per 100 cells/µL), recorded using flow cytometry and fluorescent monoclonal antibody analysis (Beckman Coulter, Inc., Mississauga, Ontario, Canada), and at most recent date prior to survey; ART adherence, measured on the basis of prescription refill compliance (240), defined as the number of days ART was dispensed over the number of days an individual was eligible for ART, in the past 12 months (≥95% vs. <95%), at most recent date prior to survey. This variable has shown to reliably predict survival among IDU in previous studies (72, 240). All potential explanatory variables were collected at baseline in 1998 / 1999 from the HIV/AIDS DTP enrollment survey, except where indicated above.

5.3.3 Statistical Analysis

As a first step, bivariate analyses were performed on the entire study sample at baseline, stratified by food insecurity, hunger and all-cause mortality, respectively. Pearson’s Chi-Square tests were used to compare categorical variables. In instances where counts were small (five or less), the Fisher’s Exact Test was used. Continuous variables were compared using Wilcoxon Rank Sum Test. Next, two time-updated Cox proportional hazard confounder models were constructed to determine the association between food insecurity/hunger and all-cause mortality, controlling for potential confounders. A multivariate model was built using an adaptation of methods described by Greenland and colleagues (244, 245). This manual backward stepwise approach involved first fitting a full model, including all explanatory variables, and noting the value of the coefficient associated with food insecurity/hunger. Reduced models were then constructed, each removing one secondary explanatory variable from the full set. Comparing the value of the coefficient for food insecurity in the full model and each of
the reduced models, secondary variables were removed corresponding to the smallest relative change in the coefficient for food insecurity. This iterative process continued until the maximum change of the value for food insecurity from the full model exceeded 5%. The intent of this model building strategy was to retain secondary variables in the final multivariate model with greater relative influence on the relationship between food insecurity and mortality. This technique has been previously applied in HIV-positive studies to estimate the independent relationship between a hypothesized predictor variable and clinical outcome (246, 247). This process was repeated to examine the relationship between hunger and mortality. Ad hoc tests to assess potential cohort effects on survival were not deemed necessary since participants were all recruited after the introduction of ART, which led to a homogenous trend in reductions of HIV-related mortality over time (295).

Next, stratification was performed in order to explore whether BMI was an effect modifier in the relationships between food insecurity/hunger and mortality. Data were stratified into four categories: i) not food insecure/hungry and not underweight (reference); ii) not food insecure/hungry and underweight; iii) food insecure/hungry and not underweight; and iv) food insecure/hungry and underweight. Kaplan Meir survival probability (i.e. cumulative non-occurrence of mortality) was plotted against time for each strata. The log rank test was used to compare survival curves across the four strata. If the association between food insecure/hungry and mortality varied significantly across the strata (denoted by a $p \leq 0.05$), it suggested that the effect of food insecurity/hungry on survival was modified by BMI level. All statistical analyses were completed using R v2.10.1 (R Foundation, Vienna, Austria).
### 5.4 Results

Baseline characteristics of IDU enrolled in the BC-wide HIV/AIDS DTP in years 1998/1999, stratified by food security status, are show in Table 5.1. A total of 254 individuals enrolled at baseline, responded to the food security scale question in the survey, and had consistent follow-up during the years under study. Of this analytic sample, 181 (71.26%) reported being food insecure, and 108 (42.5%) were hungry; the median age was 38.0 years [IQR: 34.0 - 43.0]; 211 (83.07%) were male; 58 (22.9%) reported Aboriginal ancestry; 219 (96.9%) had a BMI above 18.5 kg/m². The median CD4 cell count was 380.0 per 100 cells/µL (IQR: 220.0 – 510.0); the median viral load was 2.6 log₁₀ copies/mL (IQR 2.6 - 3.7); 63 (24.8%) were diagnosed with AIDS; and 123 (48.4%) were ≥95% adherent to ART in the 12-months preceding enrollment. During the study period (between June 21, 1998 and Sept 30, 2011), a total of 105 (41.34%) individuals died. Bivariate comparison of participant characteristic by food security status revealed that individuals with lower incomes, receiving a PI-based regimen, and initiating ART at a later year, were all significantly more likely to be food insecure (p < 0.05). Baseline characteristics among HIV-positive individuals initiative ART, stratified by all-cause mortality, are presented in Table 5.2. A total of 87 (48.1%) of individuals who reported being food insecure died over the study period, compared to 18 (24.7%) among individuals who reported being food secure (p = 0.001); and a total of 54 (51.4%) individuals reporting hunger died, compared to 54 (36.2%) reporting no hunger (p = 0.022).

Unadjusted and adjusted analyses of factors associated with mortality among IDU are presented in Table 5.3. In unadjusted analyses (Column 1), participants who were food insecure were over twice as likely to die, compared to individuals who were food secure (HR = 2.41, 95% CI: 1.45 – 4.01, p < 0.001); and participants who were
hungry were almost twice as likely to die (HR = 1.78, 95% CI: 1.21 - 2.61) compared to individuals with no hunger. Other factors significantly associated with all-cause mortality included Aboriginal ancestry, low income, <95% adherence to ART, lower median CD4 cell count and higher median plasma HIV RNA. In adjusted analyses, controlling for potential confounders, food insecurity remained significantly associated with all-cause mortality (AHR = 1.95, 95% CI: 1.07 – 3.53) (Column 2), and hunger was no longer significant (AHR = 1.05, 95% CI: 0.65 – 1.70) (Column 3). Additional factors associated with increased likelihood of death in the model examining food insecurity included having an annual income >$15,000, Aboriginal ancestry, and a higher median viral load. In the model exploring hunger, additional characteristics associated with higher risk of mortality included older age, annual income >$15,000 and a higher median viral load.

Crude Kaplan-Meir survival probabilities for IDU in this BC-wide cohort, stratified by food insecurity and hunger status are presented in Figure 5.1a and 5.1b, respectively. Consistent with findings from the bivariate analysis, individuals reporting food insecurity/hunger had low probability of survival, compared to individuals who were food secure/not hungry. Crude Kaplan-Meir survival probabilities for IDU, stratified by food insecurity/hunger and BMI level are presented in Figure 5.2a and 5.2b, respectively. Due to the limited number of people with low BMI in the overall study sample, p-values for stratified Kaplan-Meir survival probabilities were uninterpretable, and prohibited further exploration of potential modifying effect of BMI in the relationship between food insecurity/hunger on all-cause mortality in multivariate models.

5.5 Discussion

This study was the first to examine the potential relationship between food insecurity and hunger on mortality among HIV-positive IDU. After 13.3 years of follow-
up, individuals who reported being food insecure at baseline had a two-fold increased risk of mortality, when controlling for potential confounders. Food insufficiency was associated with increased risk of death in univariate analysis, but the association was no longer significant after controlling for potential confounders in adjusted analyses. The former results are consistent with results from a study in the same setting which found a significant association between food insecurity and non-accidental mortality among individuals receiving ART across BC (65). The current analyses build on this previous study by differentiating between food insecurity and hunger, and suggest that factors other than insufficient food consumption may be driving the relationship between food insecurity and excess mortality in this sub-population.

Crude survival probability, stratified by food security and BMI level, suggest a similar pattern of association as found previously in this setting by Weiser et al. Among 1,119 HIV-positive individuals initiating ART in BC, individuals reporting food insecurity and low BMI had 94% increased odds of non-accidental death after eight years of follow-up (65). A large body of evidence has found that weight loss and wasting are strong independent predictors of mortality, even in the ART era. Lower BMI at time of HIV diagnosis been found to be a strong independent predictor of survival (276). Poor nutritional status, including weight loss, low BMI, micronutrient biomarkers (i.e. hemoglobin) and middle upper arm circumference (MUAC) values have been associated with increased risk of mortality in early months following ART initiation (279, 283, 296). Linear trends in mortality have been observed with increasing grades of malnutrition among individuals receiving ART (168, 277), with weight loss of over 10% being associated with 4-6 fold increases in mortality (277). Among IDU, the adverse impacts of low BMI on mortality are exacerbated by Hepatitis C virus (HCV), which has been found to be seven times higher among HIV-positive IDU, compared to non-IDU in the province of BC (297). HCV is known to increase individual resting energy expenditure (298), and
incur changes in body composition, including weight loss (299, 300), particularly among active illicit drug users (40). Treatment regimens for HCV additionally incur weight loss (301), which may place co-infected individuals at heightened risk of adverse health outcomes. Low BMI, in turn, has been associated with renal disfunction (302), and has been shown to independently predict mortality among co-infected individuals (303). This study was insufficiently powered to detect the modifying effect of undernutrition on the relationship between food insecurity and all-cause mortality. Further studies are essential to examine this potential mechanism, and to examine the additional role of HCV co-infection in this relationship.

The finding that food insecurity, and not hunger, was significantly associated with all-cause mortality suggests that other aspects of food insecurity, measured within the Radimer/Cornel scale (Appendix 2), may be driving this association, including poor dietary diversity and/or anxiety regarding food access. Food insecurity is theorized to be linked to adverse HIV-related outcomes through diverse nutritional, mental health and behavioral pathways (24). Macro- and micronutrient deficiencies, which represent an extreme consequence of, and surrogates markers for, poor dietary diversity (Chapter 2) have been associated with mortality among HIV-positive individuals in the ART era. Compared to non-IDU, active IDU may be at increased risk of developing nutrient deficiencies due to metabolic abnormalities and nutrient interactions associated with drug use (34). Studies have found that low albumin and phosphate levels have been associated with early mortality among malnourished individuals initiating ART (280, 282). Deficiencies in zinc, Vitamin A, iron and B₁₂ have also been associated with increased risk of HIV-related mortality in illicit drug using populations (34, 278, 284, 304). Selenium deficiency has shown to be a particularly strong predictor of death, having been associated with a 20-fold increase in risk of mortality among HIV-positive IDU (34). The adverse impacts of poor dietary diversity and nutrient status on death may also be
compounded by the presence of HCV co-infection in this population. The relationship between nutrient intake and risk of excess mortality among HCV co-infected individuals has been confirmed by studies that have found that Vitamin A deficiency is associated with increased risk of HCV-related chronic liver disease and death (305), and that Vitamin K has a protective effect on re-occurrence hepatic carcinoma and associated mortality among HCV infected individuals (306, 307). Findings from the current study, taken together with existing evidence regarding the relationship between nutrient deficiencies and mortality among HIV-positive IDU populations, suggest an urgent need for public health bodies to evaluate the possible role of nutritional screening and supplementation to prevent excess mortality among IDU receiving ART in this setting. Operations research should explore the possible compounding effect of HCV co-infection on the relationship between nutrient deficiency and mortality, and consider evaluating the use of nutrient-rich food as an incentive for early HCV detection and treatment uptake, which has shown to be problematic in this setting (308, 309).

The observed association between food insecurity and all-cause mortality in this sample of IDU receiving ART may also be explained by mental health mechanisms. Several questions on the Radimer/Cornell scale pertain to feelings of anxiety regarding food access. It is possible that participants responding affirmatively to these food security measures may have increased odds of mental health disorders. Mental health disorders, including anxiety and depression, are commonly reported among HIV-positive populations, and believed to increase risk of mortality through both behavioural and biologic mechanisms. Symptoms of depression have been associated with poor virologic response (310-312), reduced immunologic capacity (313), AIDS and non-AIDS related death, among individuals on ART (247, 314-317). Feelings of guilt, fear and discrimination have been associated with delayed access to HIV treatment and care (318), and non-adherence to ART (319-321). A recent study of 9,003 HIV-positive
individuals in the US found that presence of mental health disorders, including schizophrenia and bi-polar disorder, were significantly associated with all-cause mortality (322). Taken together, findings from this analysis and evidence of the linkages between mental health disorders and mortality among HIV-infected populations suggest a need to evaluate the possible role of comprehensive mental health support in the context of existing harm reduction and HIV treatment services in order to prevent excess mortality.

This study has several strengths and limitations that warrant consideration. Participants were not randomly selected, and therefore are not representative of the HIV-positive general or IDU populations in BC. Common to all survival analyses, the censoring of participants who were either event-free or lost to follow-up may have led to an underestimation of true time to event. Longitudinal data was not available for most socio-demographic and clinical variables, including food insecurity, hunger and BMI. It was therefore unable to ascertain the possible time-updated effects of food insecurity/hunger on mortality. Information bias, and specifically responder bias, may have led to non-differential misclassification of hunger status, biasing OR estimates towards the null. Self-reported nutritional estimates have shown to be less reliable than clinical nutrition markers. While the measure of food insufficiency or hunger used in this study has been extensively validated in low income populations (38, 64, 248), future studies could be strengthened by applying robust dietary intake assessment methods validated for use among HIV-positive individuals, including 24hr dietary recall and food frequency questionnaires (269, 270). It is possible that nutritional status measures used in this study led to an overestimation of the proportion of underweight participants in this sample. Self-reported measures of BMI have shown to be less reliable than clinical nutrition markers, due to under-reporting of weight, of over-reporting height (268), and varying responses by gender and beliefs of social desirability (268). Future studies could be strengthened by clinical assessment of body weight loss, body cell mass and
subjective assessments of global nutritional status, which have found to be robust among people living with HIV/AIDS (292), and body composition and biochemical measures commonly used in HIV-positive IDU populations (270). Residual confounding - due to dichotomization of continuous variables, use of surrogate markers, misclassification, or failure to account for unobserved/unknown confounders – may have introduced bias into effect estimates. Future studies could be strengthened by considering the potential confounding impact of geographic region on the relationship between hunger and mortality, which has been independently associated with both HIV-related food insecurity (data not published) and mortality trends in BC (295).

This study found that food insecurity was associated with a two-fold increased risk of mortality, after controlling for potential confounders, among HIV-positive IDU receiving ART across BC, Canada. The finding that hunger was not significantly associated with mortality in adjusted analyses suggests that the association between food insecurity and mortality may be driven by factors other than insufficient food consumption. Further research is necessary to understand which sub-types of food insecurity are driving this association, and to examine modifying effects of diverse nutritional, mental health and behavioral factors in the relationship between food insecurity and mortality. Results from this study point towards an urgent need to strengthen social and structural supports for HIV-positive IDU, including enhanced nutritional counseling and referral for nutrient support, within harm reduction and HIV treatment programs to prevent excess mortality among IDU in BC.
Table 5.1 Baseline characteristics among HIV-positive injection drug users initiating antiretroviral therapy across British Columbia, by food security status, between June 1998 and Sept 2011 (n=254)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N (%)</th>
<th>Food Insecure 181 (71.3%)</th>
<th>Food Secure 73 (28.7%)</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, IQR³</td>
<td>38.0 (34.0 - 43.0)</td>
<td>38.0 (34.0 - 43.0)</td>
<td>38.0 (34.0 - 43.0)</td>
<td>0.933</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>211 (83.1%)</td>
<td>148 (81.8%)</td>
<td>63 (86.3%)</td>
<td>0.492</td>
</tr>
<tr>
<td>Female</td>
<td>43 (16.9%)</td>
<td>33 (18.2%)</td>
<td>10 (13.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Aboriginal ancestry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (22.9%)</td>
<td>45 (25.0%)</td>
<td>13 (17.8%)</td>
<td>0.286</td>
</tr>
<tr>
<td>No</td>
<td>195 (77.1%)</td>
<td>135 (75.0%)</td>
<td>60 (82.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Unstable housing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28 (11.8%)</td>
<td>21 (12.2%)</td>
<td>7 (10.8%)</td>
<td>0.936</td>
</tr>
<tr>
<td>No</td>
<td>209 (88.2%)</td>
<td>151 (87.8%)</td>
<td>58 (89.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Education status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ High school</td>
<td>161 (64.7%)</td>
<td>110 (61.5%)</td>
<td>51 (72.9%)</td>
<td>0.122</td>
</tr>
<tr>
<td>&lt; High school</td>
<td>88 (35.3%)</td>
<td>69 (38.5%)</td>
<td>19 (27.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Annual income</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;$15,000</td>
<td>63 (28.1%)</td>
<td>23 (14.7%)</td>
<td>40 (58.8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤$15,000</td>
<td>161 (71.9%)</td>
<td>133 (85.3%)</td>
<td>28 (41.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥18.5 kg/m²</td>
<td>219 (96.9%)</td>
<td>153 (96.2%)</td>
<td>66 (98.5%)</td>
<td>0.629</td>
</tr>
<tr>
<td>&lt;18.5 kg/m²</td>
<td>7 (3.1%)</td>
<td>6 (3.8%)</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>AIDS diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>63 (24.8%)</td>
<td>44 (24.3%)</td>
<td>19 (26.0%)</td>
<td>0.899</td>
</tr>
<tr>
<td>No</td>
<td>191 (75.2%)</td>
<td>137 (75.7%)</td>
<td>54 (74.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>ART start year</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ART use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>191 (75.2%)</td>
<td>138 (76.2%)</td>
<td>53 (72.6%)</td>
<td>0.655</td>
</tr>
<tr>
<td>No</td>
<td>63 (24.8%)</td>
<td>43 (23.8%)</td>
<td>20 (27.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>PI-based regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>154 (60.6%)</td>
<td>101 (55.8%)</td>
<td>53 (72.6%)</td>
<td>0.019</td>
</tr>
<tr>
<td>No</td>
<td>100 (39.4%)</td>
<td>80 (44.2%)</td>
<td>20 (27.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Adherence to ART</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 95%</td>
<td>123 (48.4%)</td>
<td>82 (45.3%)</td>
<td>41 (56.2%)</td>
<td>0.153</td>
</tr>
<tr>
<td>&lt; 95%</td>
<td>131 (51.6%)</td>
<td>99 (54.7%)</td>
<td>32 (43.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 cell count</strong> (per 100 cells/µL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, IQR³</td>
<td>380 (220 - 510)</td>
<td>360 (210 – 500)</td>
<td>400 (230 – 555)</td>
<td>0.149</td>
</tr>
<tr>
<td><strong>Plasma HIV RNA</strong> (per log₁₀ copies/mL)</td>
<td></td>
<td>2.6 (2.6 – 3.7)</td>
<td>2.6 (2.6 – 3.8)</td>
<td>2.6 (2.6 – 3.2)</td>
</tr>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>105 (41.3%)</td>
<td>87 (48.1%)</td>
<td>18 (24.7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>No</td>
<td>149 (58.7%)</td>
<td>94 (51.9%)</td>
<td>55 (75.3%)</td>
<td></td>
</tr>
</tbody>
</table>

1. Inter-quartile range
2. Highly active antiretroviral therapy use
3. Protease Inhibitor-based regimen
4. Within last 12 months of interview
Table 5.2 Baseline characteristics among HIV-positive injection drug users initiating antiretroviral therapy across British Columbia, stratified by all-cause mortality, between June 1998 and Sept 2011 (n=254)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total N (%)</th>
<th>All-cause mortality</th>
<th>All-cause mortality</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Yes (41.3%)</td>
<td>No (58.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>105 (41.3%)</td>
<td>94 (63.1%)</td>
<td>149 (58.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Food insecure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>181 (71.3%)</td>
<td>87 (82.9%)</td>
<td>94 (63.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>73 (28.7%)</td>
<td>18 (17.1%)</td>
<td>55 (36.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hunger</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>108 (42.5%)</td>
<td>54 (51.4%)</td>
<td>54 (36.2%)</td>
<td>0.022</td>
</tr>
<tr>
<td>No</td>
<td>146 (57.5%)</td>
<td>51 (48.6%)</td>
<td>95 (63.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.125</td>
</tr>
<tr>
<td>Median, IQR¹</td>
<td>38 (34 – 43)</td>
<td>38 (34 – 44)</td>
<td>38 (34 – 43)</td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>211 (83.1%)</td>
<td>81 (77.1%)</td>
<td>130 (87.2%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Female</td>
<td>43 (16.9%)</td>
<td>24 (22.9%)</td>
<td>19 (12.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Aboriginal ancestry</strong></td>
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<td></td>
<td></td>
<td>0.024</td>
</tr>
<tr>
<td>Yes</td>
<td>58 (22.9%)</td>
<td>32 (30.5%)</td>
<td>26 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>195 (77.1%)</td>
<td>73 (69.5%)</td>
<td>122 (82.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Unstable housing</strong></td>
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<td></td>
<td>0.213</td>
</tr>
<tr>
<td>Yes</td>
<td>28 (11.8%)</td>
<td>15 (15.5%)</td>
<td>13 (9.3%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>209 (88.2%)</td>
<td>82 (84.5%)</td>
<td>127 (90.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Education status</strong></td>
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<td></td>
<td>0.363</td>
</tr>
<tr>
<td>≥ High school</td>
<td>161 (64.7%)</td>
<td>64 (61.0%)</td>
<td>97 (67.4%)</td>
<td></td>
</tr>
<tr>
<td>&lt; High school</td>
<td>88 (35.3%)</td>
<td>41 (39.0%)</td>
<td>47 (32.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Annual income</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;$15,000</td>
<td>63 (28.1%)</td>
<td>11 (12.0%)</td>
<td>52 (39.4%)</td>
<td></td>
</tr>
<tr>
<td>≤$15,000</td>
<td>161 (71.9%)</td>
<td>81 (88.0%)</td>
<td>80 (60.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.647</td>
</tr>
<tr>
<td>≥18.5 kg/m²</td>
<td>219 (96.9%)</td>
<td>90 (95.7%)</td>
<td>129 (97.7%)</td>
<td></td>
</tr>
<tr>
<td>&lt;18.5 kg/m²</td>
<td>7 (3.1%)</td>
<td>4 (4.3%)</td>
<td>3 (2.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>AIDS diagnosis</strong></td>
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<td></td>
<td></td>
<td>0.893</td>
</tr>
<tr>
<td>Yes</td>
<td>63 (24.8%)</td>
<td>26 (24.8%)</td>
<td>37 (24.8%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>191 (75.2%)</td>
<td>79 (75.2%)</td>
<td>112 (75.2%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>191 (75.2%)</td>
<td>82 (78.1%)</td>
<td>109 (73.2%)</td>
<td>0.453</td>
</tr>
<tr>
<td>No</td>
<td>63 (24.8%)</td>
<td>23 (21.9%)</td>
<td>40 (26.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>PI-based regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.062</td>
</tr>
<tr>
<td>Yes</td>
<td>154 (60.6%)</td>
<td>56 (53.3%)</td>
<td>98 (65.7%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100 (39.4%)</td>
<td>49 (46.7%)</td>
<td>51 (34.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Adherence to ART</strong></td>
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<td></td>
<td></td>
<td>0.008</td>
</tr>
<tr>
<td>≥ 95%</td>
<td>123 (48.4%)</td>
<td>40 (38.1%)</td>
<td>83 (55.7%)</td>
<td></td>
</tr>
<tr>
<td>&lt; 95%</td>
<td>131 (51.6%)</td>
<td>65 (61.9%)</td>
<td>66 (44.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>CD4 cell count</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.029</td>
</tr>
<tr>
<td>Median, IQR¹</td>
<td>380 (220 – 510)</td>
<td>320 (180 - 470)</td>
<td>410 (235 – 540)</td>
<td></td>
</tr>
<tr>
<td><strong>Plasma HIV RNA</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median, IQR¹</td>
<td>2.6 (2.6 – 4.0)</td>
<td>3.0 (2.6 – 4.1)</td>
<td>2.6 (2.6 – 3.1)</td>
<td></td>
</tr>
</tbody>
</table>

1. Inter-quartile range
2. Highly active antiretroviral therapy use
3. Protease Inhibitor-based regimen
4. Within last 12 months of interview
Table 5.3 Unadjusted and adjusted factors associated with all-cause mortality among HIV-positive injection drug users initiating highly active antiretroviral therapy in British Columbia, between June 1998 and Sept 2011 (n=254)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unadjusted model HZ(^1) (95% CI)(^2)</th>
<th>Adjusted model including food insecurity AHZ(^3) (95% CI)(^2)</th>
<th>Adjusted model including hunger AHZ(^4) (95% CI)(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food insecure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>2.41 (1.45 – 4.01)</td>
<td>1.95 (1.07 – 3.53)</td>
<td>--</td>
</tr>
<tr>
<td>Hunger</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>1.78 (1.21 - 2.61)</td>
<td>--</td>
<td>1.05 (0.65 – 1.70)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 10 year increase</td>
<td>1.19 (0.94 – 1.50)</td>
<td>1.27 (0.98 – 1.65)</td>
<td>1.46 (1.09 – 1.94)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs. female</td>
<td>0.64 (0.41 – 1.01)</td>
<td>--</td>
<td>0.59 (0.34 – 1.02)</td>
</tr>
<tr>
<td>Aboriginal ancestry</td>
<td>Yes vs. no</td>
<td>1.92 (1.27 – 2.92)</td>
<td>2.15 (1.34 – 3.45)</td>
</tr>
<tr>
<td>Unstable housing</td>
<td>Yes vs. no</td>
<td>1.50 (0.87 – 2.60)</td>
<td>--</td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;High school vs. ≤high school</td>
<td>0.85 (0.57 – 1.25)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Annual income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;$15,000 vs. ≤$15,000</td>
<td>0.27 (0.14 – 0.50)</td>
<td>0.33 (0.16 – 0.68)</td>
<td>0.28 (0.14 – 0.58)</td>
</tr>
<tr>
<td>AIDS diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>0.95 (0.61 – 1.49)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥18.5 kg/m(^2) vs. &lt;18.5 kg/m(^2)</td>
<td>0.74 (0.27 – 2.01)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>ARV start year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per year increase</td>
<td>1.03 (0.93 – 1.14)</td>
<td>0.88 (0.78 – 1.00)</td>
<td>0.93 (0.81 – 1.06)</td>
</tr>
<tr>
<td>ART use (^5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>1.21 (0.76 – 1.93)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>PI-based regimen (^6)</td>
<td>Yes vs. no</td>
<td>0.69 (0.47 – 1.01)</td>
<td>--</td>
</tr>
<tr>
<td>Adherence to ART (^7)</td>
<td>≥95% vs. &lt;95%</td>
<td>0.59 (0.40 – 0.87)</td>
<td>--</td>
</tr>
<tr>
<td>CD4 cell count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 100 increase</td>
<td>0.89 (0.82 – 0.98)</td>
<td>0.96 (0.87 – 1.06)</td>
<td>0.96 (0.86 – 1.07)</td>
</tr>
<tr>
<td>HIV RNA viral load</td>
<td>Per Log(_{10}) increase</td>
<td>1.50 (1.23 – 1.84)</td>
<td>1.42 (1.12 – 1.80)</td>
</tr>
</tbody>
</table>

1. Hazard Ratio
2. 95% Confidence Interval
3. Adjusted Hazard Ratio
4. Highly active antiretroviral therapy
5. Protease Inhibitor
6. Within the last 12 months of interview
**Figure 5.1a** Crude cumulative incidence of all-cause mortality among HIV-positive injection drug users initiating antiretroviral therapy, stratified by food security status

![Graph showing cumulative incidence of mortality among HIV-positive injection drug users stratified by food security status.]

- Food secure: N = 73
- Food insecure: N = 181

**Figure 5.1b** Crude cumulative incidence of all-cause mortality among HIV-positive injection drug users initiating antiretroviral therapy, stratified by hunger status

![Graph showing cumulative incidence of mortality among HIV-positive injection drug users stratified by hunger status.]

- No hunger: N = 108
- Hunger: N = 146
Figure 5.2a Crude cumulative incidence of all-cause mortality among HIV-positive injection drug users initiating antiretroviral therapy, stratified by food security and body mass index levels

![Figure 5.2a](image1)

Figure 5.2b Crude cumulative incidence of all-cause mortality among HIV-positive injection drug users initiating antiretroviral therapy, stratified by hunger and body mass index levels

![Figure 5.2b](image2)
CHAPTER 6: SUMMARY DISCUSSION, RECOMMENDATIONS, FUTURE DIRECTIONS

6.1 Synopsis

Chapter 6 summarizes salient findings from the four studies presented in this dissertation. It describes the unique contributions of results to conceptual understandings of risk environment, food utilization and access, the linkages between food insecurity and HIV clinical outcomes, and operational concepts of HIV treatment as prevention. Chapter 6 describes strengths and limitations common to all studies, pertaining specifically to applied measurement tools, sampling methodology, study design and analytic techniques. It discusses possible application of findings to public health policy and practice by critically evaluating results in light of causal theory, and by framing recommendations within public health frameworks of risk environment and HIV treatment as prevention. The Chapter concludes by suggesting potential research directions to address current study limitations and knowledge gaps, with an emphasis on employing community-based, longitudinal and meta-analytic techniques.

6.2 Summary of Findings

The overall aim of this dissertation was to identify the current prevalence, risk factors and impacts of food insecurity/hunger on clinical outcomes among HIV-positive individuals, and particularly among illicit drug users, receiving ART in BC. The qualitative review and empirical analyses in this dissertation drew on an adapted risk environment framework to understand individual and (social, physical, physical and policy) environmental factors influencing food insecurity and associated harms among illicit drug users in BC. Within this adapted risk environment framework, the WFP conceptual
framework was used to frame the operational definition of food insecurity at the individual and household levels (i.e. food utilization and access); a framework developed by Weiser et al. was employed to guide understandings of the bi-directional linkages between food insecurity and HIV clinical outcomes; and the HIV treatment as prevention concept promulgated by Montaner et al. was used to contextualize study objectives and interpret outcomes within a public health lens.

Chapter 2 applied a scoping review technique to amalgamate and summarize salient definitions and measures of food insecurity, and to describe published evidence regarding the potential impacts of food insecurity on diverse HIV outcomes in low and high resource settings. Drawing the WFP’s operational definition of food security, this review explored food utilization and access ‘dimensions’ of food insecurity (45, 46). This review found that a mounting body of evidence exists regarding the relationship between food insecurity and vertical and horizontal HIV transmission, access to HIV treatment and care, adherence to ART, pharmacokinetic effectiveness of ARVs, immunologic and virologic responses to ART, and survival. Potential causal relations between food insecurity and these outcomes were explained by theorized nutritional, mental health, and behavioral pathways (24). Chapter 2 concluded by summarizing salient gaps in literature, and by emphasizing the need to pursue operations research in the context of integrated HIV and food security interventions, and to generate evidence that is context- and population-specific.

Chapter 3 assessed the prevalence and correlates of general food insecurity among HIV-positive individuals exposed to ART in the BC-wide LISA study. This cross-sectional analysis found that 71% of individuals in the LISA study were food insecure, and 37% were hungry. The prevalence of food insecurity in this study sample of hard-to-reach individuals was found to be approximately seven times higher than in the Canadian general population (177), and 23% higher than in a separate cohort of HIV-
positive individuals receiving ART in BC 10 years earlier (56). This analysis found that food insecurity was associated with several socio-demographic, behavioral and clinical factors including younger age, having an annual income below $CAD 15,000/year, illicit drug use, tobacco smoking and symptoms of depression. Chapter 3 concluded that future research is required to ascertain whether food insecurity is having an adverse impact on HIV treatment outcomes among specific vulnerable groups, and notably among illicit drug users.

Chapter 4 examined the relationship between hunger and plasma HIV RNA suppression among illicit drug users receiving ART in the Metropolitan Vancouver-based ACCESS cohort. This cross-sectional analysis found that approximately 64% of illicit drug users reported being hungry, and 59% had plasma HIV RNA viral load <50 copies/ml. A strong inverse association was detected between hunger and virologic suppression in univariate analysis, but this was no longer significant after controlling for potential confounders in multivariate models. This study called for further examination of the relationship between food insufficiency, adherence and virologic outcomes among illicit drug users in larger or pooled studies, to understand the potential impact of food insecurity on individual and public health goals of \textit{HIV treatment as prevention}. It additionally suggested that illicit drug users would benefit from specialized structural interventions, including food support, to reduce hunger-related harms caused by environmental risk factors.

Chapter 5 assessed the impact of food insecurity and hunger on time to all-cause mortality among HIV-positive IDU receiving ART in the province-wide HIV/AIDS DTP. This study found that 71% of participants were food insecure, 43% were hungry, and 3% were underweight at baseline in 1998. Over a median follow-up time of 13.3 years, 41% of participants died. Food insecurity was independently associated with a two-fold increased risk of mortality in this study sample, after controlling for potential
confounders. Hunger was associated with increased risk of death in univariate analyses, but no longer significant after adjustment in multivariate analyses. Crude Kaplan Meier estimates stratified by food security/hunger and BMI level, suggested that low weight may be an effect modifier in this relationship. However, the study was inadequately powered to generate meaningful results. These findings suggested that the relationship between food insecurity and all-cause mortality may be explained by factors other than insufficient food consumption, such as poor dietary diversity and anxiety regarding food access. The discussion called for an urgent need to understand the sub-types of food insecurity driving increased risk of mortality among HIV-positive IDU in this setting, and to evaluate the possible role of nutritional and mental health supports within existing harm reduction and HIV treatment programs to prevent excess death in this vulnerable group.

6.3 Unique Contributions

The unique contributions of individual studies in this dissertation have been described in Chapters 2-5. This section will summarize the novel insights these studies have collectively brought to conceptual frameworks employed in this dissertation, and to overall understandings of the relationship between food security and HIV/AIDS.

The literature review and empirical analyses in this dissertation deepened understandings of all four conceptual frameworks used in this study. Chapter 2 presented a novel overview of food insecurity definitions in the context of HIV, expanding those previously developed by international agencies. Building on the UN definition of food insecurity, the review considered not only the concepts of food insufficiency and poor dietary diversity, but also food safety, which had been previously overlooked by UN and US policy documents describing the inter-linkages between food security and
HIV/AIDS. This novel contribution to literature has been incorporated into a new conceptual framework which is being endorsed by the WFP and USAID, and which will be co-published (see Preface).

Empirical studies presented in this dissertation (Chapters 3-5) advanced understandings of the risk environment conceptual framework (42, 43). Previous reviews of social and structural barriers to effective HIV treatment among illicit drug users have mentioned food security (29, 61, 62), but had limited evidence to draw upon. Findings from this dissertation contributed to a novel understanding of how high levels of food insecurity and hunger have increasingly become important factors within the broader risk environment of illicit drug users (Chapter 3), and in turn, how food insecurity may be affecting HIV treatment outcomes among IDU receiving ART directly or through interactions with social, structural and environmental factors operating within the local risk environment (Chapters 4 and 5). Empirical results presented in this dissertation have expanded epistemological understandings of the risk environment framework, by outlining how food insecurity and hunger act as drug-related harms and as impediments to effective HIV treatment among illicit drug users.

Studies in this dissertation, and particularly the survival analysis in Chapter 5, serve to inform theoretical understandings regarding potential pathways linking food insecurity and mortality among illicit drug users. Chapter 5 was the first study to identify food insecurity as an independent predictor of mortality among IDU, and to suggest that factors other than food insufficiency may be driving this association. While findings from this study could not confirm which causal pathways were at play in the relationship between food insecurity and excess mortality among IDU receiving ART, they supported existing evidence regarding potential nutrient- and mental health-specific pathways that have been theorized to link food insecurity and adverse HIV outcomes (24), and clarified areas of focus for future etiologic research.
Finally, results from this dissertation contributed to an improved understanding of the potential role of food insecurity within the public health framework of *HIV treatment as prevention*. The literature review in Chapter 2 identified several studies that found a strong association between food insecurity and virologic non-suppression among individuals receiving ART in high resource settings, and empirical analyses in Chapter 4 found a marginal independent association between hunger and virologic non-suppression among illicit drug users receiving ART in Vancouver. These findings suggest an urgent need to explore the impacts of food insecurity/hunger on virologic suppression in pooled studies in order to inform provincial *HIV treatment as prevention* public health strategies, and international initiatives supporting WHO’s Treatment 2.0.

6.4 Strengths and Limitations

Strengths and limitations of analyses in this dissertation have been described in Chapters 3-5. The section will review strength and limitations common to all studies with regard to measurement tools, sampling methodology and study design, and analytic techniques.

6.4.2 Measurement Tools

Several strengths and limitations exist pertaining to the Radimer/Cornell measurement tool used in all empirical studies of this dissertation. The food security scale applied in Chapter 3, and individual hunger measure applied in Chapters 4 and 5 have been extensively validated throughout the US and internationally (Appendix 2). However, they have not been widely validated in Canada, among ethnic minorities, or among people living with HIV/AIDS. It is therefore possible that these measures do not adequately reflect the lived realities of people experiencing food insecurity in BC, who
have a unique socio-demographic and economic profile compared to the rest of Canada (57); or of food insecure people living with HIV/AIDS, and notably of illicit drug users (37, 56). Although general validation of the Radimer/Cornell scale likely reduced the potential for information bias, lack of validation among HIV-populations may have led to non-differential misclassification of food insecurity status. This would have led food insecure participants to be equally misclassified among exposed and non-exposed groups, biasing adjusted measures of association towards the null. Future studies seeking to examine food insecurity and hunger among people living with HIV/AIDS should consider further validation of the Radimer/Cornell scale among people living with HIV/AIDS. Where logistically and financially feasible, future studies should also consider the collection of objective markers of nutritional intake and status, using combined techniques such as anthropometry, 24-hour recall, food frequency questionnaires and laboratory bio-markers. A review of these techniques and considerations for their implementation among people living with HIV/AIDS can be found in a recent review by Fielden et al (83).

### 6.4.3 Sampling Methodology and Study Design

Several strengths and limitations exist pertaining to the sampling methodology and study designs of cohorts explored in this study. LISA and ACCESS study participants (Chapter 3 and 4) were not randomly recruited, and therefore cannot be considered representative samples of the populations under study. Extensive community- and clinic-based snowball sampling techniques aimed to minimize selection bias as much as possible, but also led to oversampling in the Vancouver DTES (70-72). Given the unique social and structural context of BC, including the presence of universal health care and fully subsidized ART use, findings from these studies should not be
generalized elsewhere. The modest financial incentive given to LISA and ACCESS participants may have introduced selection bias by increasing the probability of sampling individuals who are food insecure, thus inflating food security prevalence estimates. However, application of an abbreviated (conservative) version of the Radimer/Cornell scale (as described above) likely cancelled-out this bias. Finally, studies examined in this dissertation all had observational designs, and therefore could not infer causation. That being said, statistical associations in observational studies can, under limited circumstances, be interpreted as potentially causal if specific criteria are met, and should be given consideration by public health bodies (see Section 6.5.1).

6.4.4 Analytic Techniques

Several strengths and limitations exist pertaining to analytic techniques used in the studies of this dissertation. In order to facilitate interpretation of findings in empirical studies (Chapters 3-5), some socio-demographic and behavioral continuous variables were dichotomized. This may have incurred loss of information, resulting in reduced measurement precision, an underestimation of effect size, and decreased statistical power for detecting true relationships (257, 323-325). Where possible study methods followed guidance regarding the selection and reporting of dichotomized variables, which compliment the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (326, 327). An important strength of the logistic regression techniques used in Chapters 4 and 5 is that they prioritized elimination of bias over parsimony. The confounder model in Chapter 4 intentionally excluded the use of automated selection procedures, and employed a conservative manual backward selection technique, which reduced risk of bias from residual confounding. Additional logistic regression models drew on DAG methodology (Appendix 3) to confirm that effect
estimates were free of ‘confounder selection bias’. Chapters 3 and 4 calculated VIF values to assess potential multi-collinearity of each variable selected for final models. All values were below the ‘rule of thumb’ threshold (i.e. VIF <10) (328), suggesting that multi-collinearity was not unduly influencing the least square estimate. Ridge regression and principal components logistic regression would have enabled an evaluation of multi-collinearity with smaller mean square error (328, 329), particularly for binary predictor variables (329), but were outside the scope of this dissertation.

6.5 Application of Research Findings

The translation of research findings into policy and practice requires consideration of many issues, including cost-effectiveness, and logistic, cultural, legal and political feasibility. From an epidemiological perspective, the application of results to public health policy additionally requires rigorous consideration of hypothesized etiologic pathways and epidemiologic frameworks (258). To this end, this section will briefly review the etiologic and public health relevance of statistical associations observed in this dissertation; discuss findings in the context of the risk environment and HIV treatment as prevention public health frameworks; and will recommend policy and programmatic initiatives to optimize health outcomes of people living with HIV/AIDS in BC.

6.5.1 Etiologic and Public Health Considerations

The translation of research findings into public health policy and practice often rests on an assumption that observed statistical associations represent causal relationships (258). The reality is, however, that experimental studies needed to infer
causation are often not logistically, financially or ethically feasible. Findings from observational studies have therefore played a critical role in informing public health interventions. In the field of food security and nutrition, international agencies have relied heavily on evidence from observational studies to inform their programmatic and clinical guidelines regarding the provision of food and nutritional support (75, 330, 331). Similarly, in the field of HIV/AIDS, findings from observational studies have influenced the development of clinical guidelines regarding ART initiation, regimen type and tolerability (332).

The use of observational study findings to inform public health policies requires careful scrutiny of evidence. At the core of this critical evaluation is the need to ascertain whether observed statistical associations represent true causal relationships, or whether they are confounded by the presence of other measured or unmeasured factors. Epidemiologists have typically drawn on guidelines, known as Hill’s criteria, to ascertain when a statistical association in observational studies may be causal (258, 333). Although modern epidemiologists agree that several of these criteria are inherently flawed, there is general consensus that some have practical utility – namely, *temporality, strength of association, dose response, biologically plausibility and consistency* (245, 258, 333). Applying Hill’s criteria to findings from Chapter 5, for example, it could be argued that the statistical association observed between food insecurity and all-cause mortality among HIV-positive IDU receiving ART represented a causal relationship on the basis that it was: identified *temporally*; was statistically significant or *strong*; *biologically plausible* on the basis of known nutritional and mental health pathways (24); and *consistent* with the only other published study on this topic (65).

From a public health perspective, the notion that food insecurity may be causally related to increased risk of mortality among people living with HIV/AIDS does not preclude the importance of other risk factors known to be associated with mortality, but
draws attention to a potentially important mechanism than can be intervened upon. As an individual risk factor, food insecurity is likely not a sufficient or necessary cause of mortality among people living with HIV/AIDS in BC (333, 334). Rather, it likely acts jointly with a constellation of other risk factors to create a “set of minimal conditions and events” that inevitably produced mortality in this population (335). Within the epidemiological "sufficient-component cause” model of causation (336), the removal of any one causal component from a ‘sufficient cause’ constellation, such as food insecurity, should have a preventive impact on a disease outcome by virtue of disrupting the “set of minimal conditions” required for the outcome to manifest (258). Expanding this logic to current and previous (65) findings regarding the association between food insecurity and mortality in BC, it follows that: the elimination of food insecurity among people living with HIV/AIDS should have preventive impact on excess mortality, and should be an urgent public health priority across BC.

6.5.2 Intervention and Policy Recommendations

Assuming then that the elimination of food insecurity among people living with HIV/AIDS in BC should be an important public health goal, programs and policies need to consider whether it is more effective to intervene at the proximal or distal level. Traditional, reductionist approaches to epidemiology emphasize that intervening upon proximal causes of disease are most effective for altering health outcomes among individuals. Social-determinant approaches to epidemiology, on the other hand, highlight the importance of addressing distal causes of adverse health outcome to achieve a broader, population-level impact (334). This section will argue that the elimination of food insecurity and associated adverse HIV outcomes among individuals receiving ART in BC requires both approaches. That is, it requires strategies that optimize ART use at the
individual level, and social and structural changes that reduce drug-related harms at the 
environmental level. This section draws on the *HIV treatment as prevention* and *risk 
environment* frameworks to contextualize intervention and policy recommendations, 
which are presented here as “food for thought”.

As described previously, the universal expansion of ART access has become a 
public health priority in BC and globally in order to reduce widespread HIV-related 
morbidity, mortality, and population-level HIV incidence (Appendix 1). The STOP 
HIV/AIDS initiative in the province (53) and ‘Treatment 2.0’ initiative globally (337) 
emphasize that effective clinical management of ART at the individual-level is crucial to 
achieving broader public health goals of *HIV treatment as prevention*. Current HIV 
treatment guidelines outline several key areas of clinical care, including: timely ART 
uptake; ongoing monitoring of virologic and immunologic response, drug resistance and 
toxicities; screening and management of chronic renal disease, HCV/HBV, opportunistic 
infections and pregnancy (73). While international guidelines have emphasized the 
importance of meeting the nutrient needs of people living with HIV/AIDS as part of a 
comprehensive HIV treatment and care strategy (75, 330, 338), these have been 
implicitly interpreted as most relevant to low-resource settings where food insecurity and 
malnutrition are endemic. Findings regarding the association between food insecurity 
and mortality among people living with HIV/AIDS in BC (65) and specifically among IDU 
in this setting (Chapter 5), taken together with evidence regarding the impact of nutrient 
deficiencies and HCV-related nutritional abnormalities on mortality, suggest that 
clinicians in BC should consider nutritional screening and, where appropriate, referral for 
nutritional support, as part of therapeutic standard of care.

Under the *risk environment* framework, public health interventions seeking to 
prevent drug-related harms among substance users emphasize the importance of 
modifying physical, structural and social drug-using environments, as opposed to
individual-level knowledge and behaviors (339). Harm reduction initiatives may constitute non-drug or non-health-focused activities (43), and have shown to be most effective if they are “locally produced” (42), user-friendly and low-threshold (340). While studies in this dissertation have highlighted the elevated burden of food insecurity and hunger among HIV-positive illicit drug users, a recent study suggests that HIV-negative drug users may be at equal risk of this drug-related harm. An assessment of the prevalence and correlates of hunger among HIV-negative illicit drug users in Metropolitan Vancouver found that 65% reported being hungry and unable to afford enough food (68), a prevalence level almost identical to that found among HIV-positive illicit drug users in the same setting (Chapter 4). These findings suggest that factors operating within the risk environment of drug users in BC may be placing this population, irrespective of HIV status, at risk of food insecurity, hunger and associated harms.

Previous studies conducted in this context have already called for the development of harm reduction interventions to address the food security needs of specific sub-groups of illicit drug users, including female sex workers (341), and street-involved youth (216). Broadening these recommendations, this dissertation calls for the systematic provision of nutritional and food security screening, counseling and support services to all illicit drug users within existing HIV and harm reduction initiatives in BC. It calls upon the BC Ministry of Health and Provincial Health Services Authority to explicitly consider the food security needs of illicit drug users in provincial policies (342, 343). Finally, it supports the added value of community-based food security activities, such as the BC Community Food Action Initiative, to reduce hunger and food insecurity among low income populations living in BC’s heightened risk environment (344).
6.6 Future Research Directions

Future research directions stemming from individual analyses have been proposed in Chapters 2-5. Building on overall results from this dissertation, this section will highlight some possible research approaches that may address existing study limitations, and strengthen overall evidence regarding the relationship between food insecurity and HIV/AIDS outcomes in BC. Specifically, this section will describe the potential roles of community-based research, longitudinal operations research, and meta-analyses of observational studies.

6.6.1 Community-based Research

Chapters 2 and 3 of this dissertation directly informed the development and successful procurement of an HIV/AIDS community-based research (CBR) grant from the Canadian Institutes of Health Research (CIHR) (# CBR-99148). This study seeks to examine the impacts of food insecurity on HIV-related outcomes of adults on and off ART across BC, Ontario and Quebec, and specifically seeks to: understand the prevalence of specific types of food insecurity (insufficiency, diversity and safety) among people living with HIV/AIDS individuals; to identify socio-demographic, behavioral and clinical correlates of food insecurity in each province; and to understand the potential impacts of specific types of food insecurity on nutritional, immunologic and virologic HIV outcomes. The study is cross-sectional, and plans to recruit a total of 2,500 participants through community-based AIDS service organizations by mid-2012. In line with the GIPA principle (Greater Involvement of People with AIDS), the study has involved people living with HIV at all stages of research design and implementation. It applies principles of CBR methodology, by encouraging reciprocal learning by community and academic
partners, empowering community stakeholders, and promoting shared decision-making and knowledge translation.

This CBR study will build on methodological limitations within, and findings from, the current dissertation in several important ways. First, the use of trained HIV-positive peer-based researchers will help to strengthen the contextual relevance and appropriateness of survey questions; improve participant recruitment from hard-to-reach groups; reduce social desirability bias of participant responses; and foster meaningful analytic approaches and interpretation of findings. The use of 24-hour recall will contribute to more robust understandings of individual caloric intake and dietary diversity; and enable context- and HIV-specific validation of epidemiologic food security and hunger measures. The large sample size will reduce the probability of sampling error, strengthening the certainty of statistical inferences. Finally, use of province-specific a priori sampling frames will enable balanced recruitment of HIV-positive individuals from varying geographic regions and population sub-groups, improving the potential generalizability of findings to HIV-positive populations across BC. Together, these methodological improvements will strengthen baseline prevalence estimates of food insecurity and its sub-components, and improve the robustness of statistical inferences regarding the relationship between food insecurity and HIV outcomes in analyses.

6.6.2 Longitudinal Operations Research

Longitudinal studies will be essential to understand individual temporal changes associated with food insecurity in BC, to delineate potential nutritional, mental health and behavioral pathways linking food insecurity and HIV outcomes (24), and to estimate the possible impacts of public health initiatives aimed at mitigating these relationships.
Longitudinal studies have several important advantages over cross-sectional studies beyond the obvious strength of enabling temporal monitoring of the order of events. Due to repeated observations at the individual-level and reduced intra-subject variability (vis-à-vis inter-subject variability), longitudinal studies have superior statistical power compared to cross-sectional studies, thus strengthening the certainty of estimates and inferences. They enable the identification of cohort effects that may bias interpretation of findings if left undetected. Finally, they allow for monitoring individual-level trends, which can in turn inform understandings of population-level change over time (345). Ideally, the pilot cross-sectional community-based study described above would form the basis of an open prospective cohort, with robust quality assurance and control measures (346). This would enable longitudinal monitoring of individual and population-level food security and nutritional status, and specifically, allow for prospective evaluation of the impact of policy and program changes on various risk environments. In particular, it would allow for the prospective evaluation of modifications to food security policy and programs within BC that consider the unique needs of illicit drug users, a sub-group found to be extremely vulnerable to food insecurity and its adverse health impacts.

6.6.3 Meta-analyses

Given that RCTs are seldom a logistically or ethically feasible to investigate the impacts of food- or nutrition-based interventions on people living with HIV/AIDS, meta-analyses of observational studies may play a pivotal role in clarifying the relationships between food insecurity and HIV outcomes, and for guiding evidence-based decisions regarding appropriate clinical and public health responses. Meta-analyses are placed at the top of hierarchies of evidence, and involve the systematic identification and synthesis of study results to generate a pooled measure of effect for an exposure/intervention on
an outcome (347). Meta-analyses of observational studies on food security and HIV/AIDS would be challenging due to tremendous variations in definitions and measures of food insecurity, in HIV/AIDS clinical endpoints and in study design, and due to possible publication biases. Guidelines and reporting checklists have been developed for the reporting of meta-analyses of observational studies (348), which may facilitate this process. Meta-analyses of individual patient data would be particularly valuable in the context of food security and HIV studies as it could allow for the identification of cost-effective interventions, which are essential to sustainability, and would help to identify groups most likely to benefit from intervention (349). As suggested already (Chapter 4), there is a specific need to explore the pooled effects of food security on HIV virologic outcomes to inform local and global efforts towards achieving individual and population-level goals HIV treatment as prevention.

6.7 Conclusion

This dissertation presents a novel and important body of research regarding the potential relationships between food insecurity and clinical outcomes among people living with HIV/AIDS. It has outlined evidence from high and low resource settings regarding the impacts of food insecurity on HIV transmission, access to ART and HIV-treatment outcomes. Examining the prevalence and correlates of food insecurity among people living with HIV/AIDS in BC, Canada, this dissertation has highlighted heightened vulnerability of illicit drug users to food insecurity due to shifts in social and physical risk environments. This dissertation has generated evidence regarding the potential relationship between hunger and virologic suppression among illicit drug users, which requires further investigation in the context of HIV treatment as prevention. Finally, it
identified food insecurity as an important predictor of all-cause mortality among illicit drug users, and highlighted the need to intervene on both proximal and distal causal pathways. Empirical studies in this dissertation have strengthened understandings of context-specific factors affecting food security and adverse HIV outcomes in BC. Collectively, they have deepened understandings of risk environment conceptual frameworks, as well as frameworks describing dimensions of food access and utilization; causal pathways linking food insecurity and HIV outcomes; and the potential role of food insecurity in public health efforts to achieve HIV treatment as prevention efforts. This dissertation draws attention to the importance of considering nutritional assessment as part of HIV therapeutic standard of care for people living with HIV/AIDS. It additionally calls for social and structural public health interventions to reduce the risk of food insecurity and hunger among people living with HIV/AIDS, and specifically among illicit drug users. Community-based and longitudinal studies and meta-analyses are urgently required to inform effective, sustainable initiatives to prevent food insecurity and its adverse consequences among people living with HIV/AIDS in BC and globally.
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APPENDIX 1: TREATMENT AS PREVENTION AND THE PUBLIC HEALTH INTERVENTION TO ‘STOP HIV/AIDS' IN BRITISH COLUMBIA

A-1.1 Treatment as Prevention

WHO estimates that for every person newly receiving HIV treatment, four people become newly infected (350). Sustained combination HIV prevention strategies are essential to curb the spread of the HIV epidemic (351). This should include aggressive deployment of proven effective strategies, including circumcision and harm reduction for drug users, applied in a culturally sensitive and rights-based fashion (352-354). Progress in other areas, such as curative therapeutic interventions, preventive vaccines and microbicides, has been less than encouraging (355). While research in these areas continues as part of a comprehensive long-term strategy to eradicate HIV/AIDS, resources are specifically targeting the aggressive roll-out proven effective strategies aimed to curb HIV/AIDS (48, 352).

Increased attention has been focused on the added preventive effect of ART as a potent new synergistic strategy to curb the growth of the epidemic worldwide (47). As such, expanded ART coverage among those in medical need offers the dual benefit of decreasing morbidity and mortality among those infected with HIV, and of decreasing the risk of HIV transmission to those susceptible. HIV-1 RNA level in plasma has been shown to be a strong determining factor of the risk of HIV transmission in any given setting (356-358). ART has shown to predictably decrease HIV-1 RNA levels in plasma, as well as in semen (359), vaginal secretions (360), and rectal tissue (361). As a result, ART can substantially decrease the risk of HIV transmission at the individual and population levels.
The impact of ART on HIV transmission has been dramatically documented within the context of mother-to-child transmission (MTCT) studies (362). Vertical transmission of HIV has indeed become exceedingly rare wherever ART-based MTCT prevention programs have been implemented (363). Similarly, pre- and post-exposure prophylaxis have been proposed as a potential safe and effective means of preventing HIV transmission in selected settings (364). Indeed, post-exposure prophylaxis represents the accepted standard of care for occupational exposure to HIV (i.e. through needle-stick injury) and for mass casualty events (365, 366). The European Project on Non-occupational Post-Exposure Prophylaxis for HIV (EURO-NONOPEP) has formulated guidelines for the use of antiretroviral post-exposure prophylaxis in the event of sexual, injection drug or other exposure to HIV (367).

Recently, the preventive role of ART was proven in the context of heterosexual transmission. An RCT involving 1,763 sero-discordant couples across sites in nine countries found that early initiation of ART was associated with a 96% reduction in HIV transmission (16). Previous observational studies have echoed similar results regarding treatment as prevention. For example, in Uganda, no HIV transmission episodes were identified among 51 couples where the index case, who was receiving ART, had a HIV-1-RNA level below 1500 copies/mL (356). A dose-response effect was also observed from a Thai study, where no cases of HIV transmission were observed in an untreated cohort when the index case's serum HIV-1-RNA was less than 1100 copies/mL (357). An observational study of Spanish sero-discordant couples showed that no HIV sero- conversions took place among sexual partners of ART-treated patients, with ART being independently associated with an 80% reduction in HIV transmission (368).

At the populational level, expanded access to ART has also shown to be associated with substantial reductions in HIV transmission (47). A study in Taiwan found a 53% (95% CI, 31%–65%) reduction in new positive HIV diagnoses after the
The widespread introduction of free ART in 1996 (369). This reduction took place against a stable rate of syphilis, used as a surrogate marker of high-risk sexual behaviour. In Uganda, expanded ART access to all clinically eligible individuals was estimated to decrease HIV incidence by 11.2% (IQR, 1.8%-21.4%) (370). In Canada, new yearly HIV infections in the province of BC fell by approximately 50% after the introduction of ART between 1996 and 1998, and has remained unchanged since then. Importantly, in contrast to Taiwan, rates of syphilis have increased steadily in BC each year since 1996 (47).

The precise extent to which ART reduces HIV transmission at the population level remains incompletely characterized (371). There are important gaps in our understanding of the effect of ART on HIV transmission among specific transmission groups and socio-economic environments. Despite these limitations, the available evidence has been compelling enough to encourage further rapid scale-up of ART coverage among those in medical need. This expansion, coupled with close monitoring of the impact of this strategy on HIV transmission in varied settings, can provide further valuable insights into the preventive effect of ART.

A-1.2 Public Health Intervention to ‘STOP HIV/AIDS’ in BC

Through a joint initiative between academia and government, the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) led the first publicly-funded operational study to examine the impacts of rapid expansion of ART access on HIV incidence. In early 2010, the BC Ministry of Health funded and launched a $48-million pilot project entitled ‘Seek and Treat for Optimal Prevention of HIV/AIDS (STOP HIV/AIDS)’. Led by the BC-CfE, and implemented in collaboration with key government stakeholders and community-based organizations, the STOP HIV/AIDS initiative aims to
expand access to HIV testing, ART, and support to hard-to-reach and vulnerable populations in the areas of the province with the highest HIV incidence and prevalence, namely: Vancouver’s Downtown Eastside (DTES) and Prince George. Retrospective time trend analyses have found a strong and statistically significant association between expanded ART uptake, reduced community viral load and decreased HIV diagnoses per year in BC (263). Mathematical modeling suggests that current efforts to expand ART access to all clinically eligible individuals in the province under 2008 IAS-USA guidelines may avert a minimum of 44% new HIV infections and avoid over CAD$ 21 million in drug-costs, over the five-year intervention period (67).

Similar implementation studies evaluating different aspects of Treatment as Prevention are currently underway across North America and sub-Saharan Africa (372). Most recently, the Chinese Centre for Disease Control and Prevention (China CDC) adopted Treatment as Prevention as part of a national HIV/AIDS strategy to control HIV/AIDS by year 2015 (53). Ongoing BC-based research and results from this novel public health initiative to STOP HIV/AIDS continues to inform evidence-based HIV programs and policies worldwide. In 2011, the concept of Treatment as Prevention received broad-based scientific acclaim and political support. Science Magazine named Treatment as Prevention as the “medical breakthrough of the year” (373), and Time Magazine cited it as the third ranked top 10 medical breakthrough of 2011 (374). In the same year, US President Barack Obama and Secretary of State Hillary Clinton endorsed Treatment as Prevention, declaring the creation of “an AIDS Free Generation” as policy priority (375). Treatment as Prevention is one of the key pillars of the UNAIDS and WHO’s Treatment 2.0, an initiative which seeks to provide leadership and technical guidance to global stakeholders for rapid, simplified roll-out of ART to clinically eligible individuals globally (52).
APPENDIX 2: RADIMER/CORNELL SCALE: THE TOOL AND ITS VALIDATION

A-2.1 Radimer/Cornell Scale

The original set of indicators used to assess food insecurity, published by Radimer (88), was slightly modified by Kendall et al. (193) based on findings from a validation study. The latter version has since remained the standard format for the Radimer/Cornell scale, and the benchmark for subsequent modifications by researchers. Table A-2.1 displays Radimer/Cornell measures of food insecurity at the household and individual (adult) level, used in the current analysis. Given that only adults participated in this study, the scale in Table A-2.1 excludes child-specific measures from the Radimer/Cornell scale. The scale used in this study contains two additional differences compared to the standardized scale. First, the household-level food anxiety component, the measure “I worry about where the next day’s food is going to come from”, was replaced with “I worry about whether the food that I can afford to buy for my household will be enough”. Second, in the individual-level qualitative component, the measure “I can’t afford to eat the way I should” was removed. The implications of these adjustments to the scale are discussed in the Strengths and Limitations section of the dissertation (Section 6.4.2).
Table A-2.1 Radimer/Cornell Scale: Household and Individual Level

<table>
<thead>
<tr>
<th>Household Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Food anxiety component</strong></td>
</tr>
<tr>
<td>• I worry whether my food will run out before I get money to buy more.</td>
</tr>
<tr>
<td>• I worry about whether the food that I can afford to buy for my household will be enough.</td>
</tr>
<tr>
<td><strong>Qualitative component</strong></td>
</tr>
<tr>
<td>• We eat the same thing for several days in a row because we only have a few different kinds of foods on hand and don’t have money to buy more.</td>
</tr>
<tr>
<td><strong>Quantitative component</strong></td>
</tr>
<tr>
<td>• The food that I bought just didn’t last, and I didn’t have money to get more.</td>
</tr>
<tr>
<td>• I ran out of the foods that I needed to put together a meal and I didn’t have money to get more.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individual (Adult) Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Qualitative component</strong></td>
</tr>
<tr>
<td>• I can’t afford to eat properly.</td>
</tr>
<tr>
<td><strong>Quantitative component</strong></td>
</tr>
<tr>
<td>• I am often hungry, but don’t eat because I can’t afford enough food.</td>
</tr>
<tr>
<td>• I eat less than I think I should because I don’t have enough money for food.</td>
</tr>
</tbody>
</table>
A-2.2 Validation of the Radimer/Cornell Scale

Diverse validation criteria can be used to ascertain whether a specific analytic measurement is valid for a given purpose and context (376). The Radimer/Cornell scale has been validated according to multiple criteria, including: being constructed on a well-grounded theory; performing consistently with understanding; and demonstrating precision, dependability, and accuracy within specified performance standards (191). The following will synopsize and update relevant findings from the validation assessment of the Radimer/Cornell scale published by Frongillo EA (191), and describe the diverse populations in which Radimer/Cornell measures have been validated.

A-2.2.1 Construction on well-grounded theory

The Radimer/Cornell scale was built on a theory of food insecurity that was grounded in extensive qualitative research about the experiences and perceptions of hunger (191). Radimer inductively derived the concept of food insecurity through a “phenomenological or naturalistic” approach, using in-depth interviews among low-income individuals in upstate New York (88). These preliminary studies found that food insecurity is experienced differently at the household, individual (adult) and child levels; and that it constitutes four components (quantity, quality, certainty and acceptability), with the first two related to physical food use and the last two related to psychological and social experiences. The study also concluded that food insecurity exists along a continuum, progressing from uncertainty and anxiety about food, to the severe manifestation of hunger from not having enough to eat (88, 192).
A-2.2.2 Construct Validity

Construct validity is the “extent to which any measuring instrument measures what it is intended to measure”, and is often assessed using principal components factor analysis with varimax and oblique rotation (377). A measurement tool is deemed well-designed if factor analysis reveals patterns in measure responses that are consistent with dimensions of the theoretical constructs it intends to assess. Studies exploring the construct validity of Radimer/Cornell measures have found that the items in the tool are consistent with its original theoretical construct (191). Several observational studies by Kendall et al. empirically confirmed that food insecurity is experienced as a progression, and that hunger is a distinct consequence of food insecurity (193, 378). Factor analysis revealed a four-factor solution, suggesting that food insecurity is experienced distinctly at the i) household and ii) child-levels, and constitutes components of iii) quality and iv) quantity within each level (193). Rotated principal component factor analysis found that Radimer/Cornell scale items revealed two factors - altered eating patterns at the household and at the child level, with a total variance of 66.2% (196).

Radimer/Cornell measures have also undergone extensive cognitive testing to determine whether question wording was commensurate with its intended meaning (87, 379, 380). These qualitative studies have found, for example, that respondents appropriately interpreted food insufficiency questions as related to severe reductions in food quantity (379). Radimer/Cornell measures have also been applied across different North American contexts to see whether the theoretical progression of food insecurity severity is reflected in the pattern of responses. A comparison of five population-based surveys in the US and Canada, containing eight Radimer/Cornell measures in common, found consistency in patterns of affirmative responses to the measures within the scale (191).
A-2.2.3 Internal Consistency

Internal consistency (or homogeneity) is an aspect of reliability and refers to the “ability of items measuring an attribute to elicit similar responses from any given respondent on a single administration” (381). It is assessed using Cronbach’s coefficient alpha, yielding a value between 0 and 1. A Cronbach alpha above 0.7 is considered acceptable, above 0.8 good, and greater than 0.9 excellent (382). Kendall et al.’s original validation study of the Radimer/Cornell scale found that the Cronbach’s alpha was 0.84 for household-level, 0.86 for individual-level, and 0.85 for child-level measures of food insecurity (193). Several subsequent studies have validated modified versions of the instrument and also found that it had good internal consistency, with Cronbach’s alphas >0.8 (195, 196).

A-2.2.4 Criterion-related Validity

Criterion-related validity, also referred to as predictive validity, is the relation between a predictor and criterion before, during or after a predictor is applied (383). Criterion-related validity is evaluated by means of comparing results from a measurement tool to criteria theorized to be associated with the concept being measured (377). Observational studies found that worsening of food security status, according to Radimer/Cornell measures, was associated with an exponential increase in the proportion of individuals engaging in food programs; with having low income, education and employment; and with significant decreases in household frequency of consumption of fruits and vegetables, and with reduced availability of food (193, 378). Other validation studies examining altered versions the Radimer/Cornell tool found that food security measures were associated with similar socio-demographics, and in the
expected directions (195, 196).

A-2.2.5  Accuracy

Accuracy can be understood as the “extent to which a measure provides unbiased assessment of the phenomena” and is determined by comparison to a criterion measure and in-depth analysis (191). The Radimer/Cornell measures were found to have good specificity, ranging between 63-71%, and excellent sensitivity, between 84-89%, compared with a criterion measure based on in-depth qualitative interviews, 24hr dietary recalls and household food inventories (384). Another study also found the measures had specificity ranging between 76-92%, and sensitivity averaging at 75% (194).

A-2.3  Validation and Use in Specific Populations

A-2.3.1  Validation in North America

Radimer/Cornell measures have been validated in diverse North American settings, including among low-income groups, households with women and children, urban and rural settings, and diverse ethnic and age groups (192-194). Much of the early research on the measurement of food insecurity and hunger was conducted in population of low socio-economic status (192, 385). For example, in one of the original studies by Radimer, half of all respondents reported receiving food stamps in the previous 12 months (192). Early studies validating the Radimer/Cornell scale focused exclusively on households with women and children (192, 193). The tool was later tested
for accuracy among elderly urban African-Americans, and rural Caucasian Americans and found to have reasonable specificity and good sensitivity (194).

**A-2.3.2 Validation Cross-culturally**

Radimer/Cornell measures have also been used and validated internationally, suggesting that the tool may be a useful estimate of food insecurity cross-culturally. The tool has been applied in Korea (386) and Russia (387), and validated for use in urban populations in Iran (195) and rural population in Tanzania (196). In Iran, a validation study based on a random sample of 250 households with women and children found that the Radimer/Cornell measures of food insecurity had good internal consistency, with Cronbach’s alphas of 0.897 for household-level food insecurity and 0.820 for individual-level food insecurity, and good criterion-related validity, particularly at the individual and childhood-levels (195). In Tanzania, a validation study among 530 women with children found that a culturally- and linguistically-modified version of the scale also had good internal consistency, with Cronbach’s alphas of 0.835 for the household-level and 0.784 for childhood-levels sub-scales of food insecurity (196).
APPENDIX 3: REVISITING CONFOUNDER SELECTION: A DIRECTEDACYCLIC
GRAPH APPROACH

A-3.1 Introduction

The study in Chapter 4 sought to examine, through cross-sectional analyses, the association between hunger and plasma HIV RNA viral load suppression among illicit drug users receiving ART in the Vancouver-based ACCESS cohort. In the Methods, secondary variables hypothesized to confound the relationship between hunger and virologic suppression were selected for inclusion in final multivariate models using a conservative backward selection procedure, described previously (244). Results from the multivariate model found that hunger was not significantly associated with virologic non-suppression. However, a growing body of epidemiologic theory suggests that use of standard techniques for adjusting for potential confounders can unintentionally introduce ‘confounder selection bias’ (271).

This Appendix will re-visit the confounder selection process used in Chapter 4 by applying DAG methodology. This Appendix begins with a description of DAGs and the definition of confounding within DAG theory. It applies DAG criteria to re-select potential confounders in the relationship between hunger and plasma HIV RNA viral load suppression, presents updated findings from multivariate logistic regression, discusses the strengths and limitations of DAGs in applied epidemiology, and the implications of findings for the results generated in Chapter 4.
A-3.2 Methods

A-3.2.1 Directed Acyclic Graphs (DAGs)

The use of DAGs is gaining momentum in epidemiology and biostatistics as a method of visualizing and understanding the complex inter-relationship between independent random variables. The primary purpose of DAGs is to depict and clarify potential causal effects between exposure(s) and outcomes (388-390). These causal diagrams have multiple uses within epidemiology. One of the main uses of DAGs has been to facilitate the identification of confounding variables (388, 390, 391); DAGs have proven to be useful to identify specific types of selection bias by means of highlighting conditional associations between exposures and outcomes (392). More recently, DAGs have been used to classify causal relationships that can give rise to different forms of effect modification (393).

Perhaps the most exciting use of DAGs is in their application to cross-sectional and longitudinal study data. Prior to data collection, DAGs can assist researchers in generating hypotheses about how variables might be causally related, and help guide decisions about what variables may be important to collect cross-sectionally or longitudinally. During data analysis, DAGs can be used to understand which variables should be controlled for in multivariable analysis (i.e. by means of stratification, statistical adjustment in regression model), on the basis of whether they constitute either: a direct or indirect causal relation; a causal relation based on a common cause; or a relation based on a common effect (391). Furthermore, they can be used to explain why certain statistically significant associations have arisen in adjusted models, and whether some observed associations may in fact be spurious. DAGs have been used by epidemiologists to demonstrate how standard statistical techniques aimed at ‘treating’
biases have at times introduced biases where none existed previously (271), and have been used to help make sense of seemingly conflicting results within observational studies (272, 273).

A DAG is composed of variables (nodes) and arrows between nodes (directed edges) such that the graph is acyclic (i.e. cannot start and end with any one node). Given a directed edge stemming from one node to another, the former is termed a ‘parent node’ and the latter a ‘child node’. A path in a DAG is a sequence of nodes connected by directed edges, regardless of arrowhead direction. Causal paths between an exposure and outcome are described as being unblocked when they are linked by either a direct or indirect (i.e. via an intermediate variable) edge. Detailed nomenclature for DAGs (389) and formalization using structural equations (388) have been described elsewhere.

A-3.2.2 DAG-theory Definition of Confounding

Methodological descriptions of DAGs emphasize that standard approaches to ‘adjusting’ for confounders (e.g. multiple regression, stratification, propensity scores) can introduce bias where none existed before due to incorrect selection of variables (271). DAG theory applies a more refined definition of confounding than traditional epidemiological methods. While still acknowledging that a confounder is a variable which is causally associated with an outcome; non-causally or causally associated with an exposure; and not an intermediate variable in the causal pathway between exposure and outcome (245, 258), DAG theory additionally stipulates that a ‘true’ confounder cannot be a descendant (effect) of the exposure or outcome (389). Implicit in this condition is what is referred to as the ‘back door criterion’, which states that that a causal pathway between a confounder and an exposure variable must constitute a directed edge
emanating from the confounder toward the exposure (389). In DAG theory, identification of a ‘true’ confounder involves visualizing the hypothesized causal inter-relationship between variables and applying the definitions/criteria above. In contexts involving many variables, robust identification confounders can be additionally facilitated by application of a six-step algorithm (274). Based on computational mathematics, this six-step approach has been successfully used to reduce bias and identify confounders in analyses considering large numbers of variables (271).

A-3.2.3 Confounder Variable Selection

A DAG was generated to visualize the theoretical causal relationships between hunger and plasma HIV RNA viral load suppression among illicit drug users, and to identify secondary explanatory variables hypothesized to confound this relationship (Figure A-3.1). This involved plotting out the relationship between all variables under examination in the proposed analysis, including secondary explanatory variables hypothesized to confound the relationship between hunger and plasma HIV RNA viral load suppression. Directed edges (i.e. pathways) between nodes (variables) were drawn based on best available evidence from published randomized clinical trials, longitudinal cohorts, (where necessary) cross-sectional studies with large sample sizes, and literature reviews. Variables meeting the DAG-theory definition of confounders were highlighted using dashed lines, and included: symptoms of depression (130, 394), daily alcohol use (395), and daily illicit drug use (injection heroin, non-injection crack/rock) (31) (Figure A-3.1).

Visualization of the hypothesized relationships between variables under examination, and comparison to DAG-theory criteria for confounders, led to the elimination of several variables that were considered potential confounders in the
relationship between food security or hunger and plasma HIV RNA viral load suppression in Chapter 4, including: money spent on drugs per day, monthly income, CD4 cell count and adherence. CD4 cell count was excluded as a potential confounder on the basis that it was identified as ‘collider variable’ (i.e. a descendant, or effect, of both hunger and plasma HIV RNA viral load suppression) (396). Spending >=$60/day on drugs and having a low monthly income were excluded on the basis that their presence theoretically precedes the onset of hunger. Adherence was excluded on the basis that it was hypothesized to be an intermediate variable on the behavioral pathway between hunger and plasma HIV RNA viral load non-suppression. The accuracy of this deductive process was double-checked by applying the six-step algorithm (271, 274) and arriving at the same conclusion. Variables finally identified as ‘true’ confounders included age, gender, homelessness, symptoms of depression and alcohol use.

**A-3.3 Results**

Multivariate analysis of factors associated with plasma HIV RNA viral load suppression among illicit drug users receiving ART are presented in Table A-3.1. Self-reported hunger was not significantly associated with plasma HIV RNA viral load suppression after controlling for age, gender, homelessness, symptoms of depression and alcohol use (AOR = 0.67, 95% CI: 0.42-1.08, p=0.098).

**A-3.4 Discussion**

Applying DAG-based methodology, this analysis found that hunger was not a significant independent predictor of virologic non-suppression among illicit drug users receiving ART. These results are consistent with those generated using standard
variable selection techniques, and suggest that the effect of ‘confounder selection bias’ was minimal in statistical analyses in Chapter 4.

The use of DAGs in the current analysis prevented the introduction of bias in several ways. The use of DAGs was instrumental in defining CD4 count as a ‘collider variable’, rather than a confounder variable. Failure to identify this would have resulted in “conditioning on a common effect”, or “collider bias” (396). Under this circumstance, controlling for CD4 count in statistical analysis would have opened an indirect path from the exposure (hunger) to the outcome (non-virologic suppression), leading to an under-estimation of the influence of hunger on plasma HIV RNA viral load suppression.

The initial DAG also identified adherence as an intermediate variable, with a direct path between hunger and non-adherence, and an indirect path from hunger to virologic non-suppression. Although, in DAG theory, it is possible to control for a variable lying on the causal pathway when estimating a total causal effect (271), in this case doing so would have introduced bias into the multivariable model. As pointed out by Kaufman et al., partitioning of a total effect into direct and indirect effects is only valid with an additional restriction that the population contains no units in which “exposure and intermediate interacts to cause the outcome” - that is, where hunger and non-adherence interact to cause a virologic non-suppression (397). In this scenario, statistical adjustment of adherence would have resulted in blockage of the indirect path (from exposure to outcome), minimizing the relationship between hunger and virologic non-suppression.

There are several important limitations to the current analysis, which are related to stipulations for use of DAG methodology. First, the construction of a DAG requires having evidence of the causal relations between variables that, by definition, can only be generated through randomized controlled trials (RCTs). The majority of studies that have examined the relationship between hunger/food security and HIV clinical outcomes have
been observational, and there remain persistent gaps in understanding about the direction of causality between these variables (Chapter 2). The DAG used in this analysis is not based exclusively on causal evidence and is therefore subject to bias. Second, DAG-theory stipulates that causal pathways between variables under investigation must be unidirectional. However, many of the relationships between variables considered in the analysis are theorized to be bidirectional, including the relationships between food security and HIV clinical outcomes (24), between food security and illicit drug use (398), and between hunger and symptoms of depression (24). Another limitation is that the DAG methodology cannot account for large number of covariates, for unmeasured confounders, and for variables that may have joint effects.

This Appendix re-examined the confounder model used in Chapter 4 to evaluate the potential relationship between hunger and plasma HIV RNA viral load suppression among illicit drug users receiving ART in the Vancouver-based ACCESS cohort. Applying a confounder selection process based on DAG-methodology, multivariate analysis did not find a significant relationship between hunger and virologic suppression. The findings are consistent with those presented in Chapter 4, suggesting that the use of standard statistical techniques for confounder selection did not introduce any significant 'confounder selection bias'.
Figure A-3.1: Hypothesized relationships between variables considered in the relationship between hunger and plasma HIV RNA suppression among HIV-positive illicit drug users receiving antiretroviral therapy in Metro Vancouver, BC
Table A-3.1 Multivariate analysis of factors associated with HIV RNA viral load suppression among HIV-positive illicit drug users receiving antiretroviral therapy in Metro Vancouver, BC (n = 406)

<table>
<thead>
<tr>
<th>Variable</th>
<th>AOR 1</th>
<th>95% CI 2</th>
<th>p - value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Self-reported hunger</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>0.67</td>
<td>0.42 - 1.08</td>
<td>0.098</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 10 year increase</td>
<td>1.95</td>
<td>1.41 - 2.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs. female</td>
<td>1.50</td>
<td>0.92 - 2.45</td>
<td>0.104</td>
</tr>
<tr>
<td><strong>Homelessness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>0.42</td>
<td>0.18 - 0.97</td>
<td>0.042</td>
</tr>
<tr>
<td><strong>Symptoms of depression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs. no</td>
<td>0.99</td>
<td>0.61 - 1.61</td>
<td>0.962</td>
</tr>
<tr>
<td><strong>Daily alcohol use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq$4 drinks vs. &lt;4 drinks</td>
<td>1.10</td>
<td>0.66 - 1.84</td>
<td>0.719</td>
</tr>
</tbody>
</table>

1. Adjusted Odds Ratio
2. 95% Confidence Interval
3. Within the last week of interview
4. Based on median split
5. Within last six months of interview