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Non-Communicable Diseases (NCDs) Among People Living with HIV (PLWH) in Cambodia

Author
Seang, Kennarey

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Non-Communicable Diseases (NCDs) Among People Living with HIV (PLWH) in Cambodia

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Epidemiology

by

Kennarey Seang

2020

ABSTRACT OF THE DISSERTATION

Non-communicable diseases (NCDs) among people living with HIV (PLWH) in Cambodia

by

Kennarey Seang
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2020
Professor Pamina M. Gorbach, Chair

Objectives: Research from high-income countries (HICs) appeared to suggest that Human Immunodeficiency Virus (HIV) and antiretroviral therapy (ART) contribute to, alongside other well-established traditional risk factors, higher prevalence of non-communicable diseases (NCDs) such as diabetes and hypertension among people living with HIV (PLWH). Many of these chronic metabolic disorders are known to increase cardiovascular disease (CVD) risk, which can be assessed using available risk stratification models. However, in certain low- and middle-income countries (LMICs), such as Cambodia, the relationship between NCDs and CVD risk and HIV is generally under-studied. This is even more so for young people living with HIV (YLWH). Therefore, I examined the relationship between NCDs and HIV among Cambodian general population and PLWH including YLWH.

Design: Cross-sectional studies.

Methods: Chapter 2 and 3 used merged data from two surveys among PLWH (n=510) and the general population (n=2747), aged between 22-65+ years, conducted by KHANA Center for Population Health Research (nongovernmental organization) in 2015 and by the University of Health Sciences in 2016, respectively. Both employed a standardized questionnaire and physical/biochemical measurement protocols developed by the World Health Organization (STEPwise Approach to Surveillance or STEP survey or STEPS). Chapter 4 employed a STEP survey to gather information on 370 YLWH, aged 18-29 years, from three HIV clinics (known as Opportunistic Infections and Antiretroviral therapy or OI/ART clinics) in Phnom Penh. The information on the young general population was then obtained from the 2016 STEP survey. For each study, we computed NCD prevalence, plus CVD risk score based on the Framingham Risk Score (FRS) equations (study 2). We performed logistic regression to examine the relationship between NCDs and CVD risk and HIV while adjusting for age, sex, residence location, behavioral risk factors (such as smoking, heavy alcohol consumption, less than 5 servings of fruits and vegetables and low physical activity) and body mass index (BMI).

Results: Chapter 2 showed that the prevalence of hypertension and high cholesterolemia among adult PLWH were lower than that of the general population. However, the prevalence of diabetes and prediabetes was higher among PLWH; the odds of prediabetes, aOR=7.30 (95% CI: 5.69, 9.36), and of diabetes, aOR=1.46 (95% CI: 0.99, 2.17), were higher among PLWH than the general population. Next, chapter 3 showed that PLWH appeared to be as likely as the general population to have moderate-to-high (estimated) 10-year CVD risk, aOR=0.88 (95% CI: 0.60, 1.29). Finally, among YLWH (chapter 4), the prevalence of diabetes and hypertension is 4% (n=16) and 6% (n=22), respectively, among YLWH, compared to 1% (n=4) and 4% (n=22), among the general population of the same age group. We observed higher odds of diabetes/prediabetes among YLWH compared with the young general population, aOR=6.64 (95% CI: 3.62, 12.19). Additionally, YLWH were at much higher odds of high cholesterolemia, aOR=7.95 (95% CI: 3.98, 15.87), than the young general population.

Conclusion: To combat a future burden of NCDs and potentially their related morbidity and mortality, our studies underlined the need to set up essential intervention strategies, be it behavioral modification or medical intervention, in order to properly address these conditions among population living with HIV including YLWH. In addition to interventions, monitoring and screening efforts should also be put in place among this population given their susceptibility to develop these conditions at a younger age than the general population.

The dissertation of Kennarey Seang is approved.

Marjan Javanbakht

Sung-Jae Lee

Ronald Brookmeyer

Vonthanak Saphonn

Pamina M. Gorbach, Committee Chair

University of California, Los Angeles

2020

Table of Contents

List of Tables

List of Figures

ABBREVIATION

LMICs	Low- and middle-income countries
NCDs	Non-communicable diseases
HIV	Human immunodeficiency virus
PLWH	People living with HIV
HICs	High-income countries
MOH	Ministry of Health
STEP	Stepwise Approach to Surveillance
CVD	Cardiovascular Disease
D:A:D	Data collection on Adverse events of Anti-HIV Drugs
FRS	Framingham Risk Score
ASCVD	Atherosclerotic Cardiovascular Disease
UHS	University of Health Sciences
KHANA	KHANA Center for Population Health Research
BMI	Body Mass Index
LDL-Chol	Low-density lipoprotein
HDL-Chol	high-density lipoproteins cholesterol
MACS	Multicenter Aids Cohort Study
TAHOD	TREAT Asia HIV Observational Database
CDHS	Cambodia Health and Demographic Survey
NHANES	National Health and Nutrition Examination survey
MMP	Medical Monitoring Project
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
HbA1C	Glycated hemoglobin
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
PIs	Protease Inhibitors
NCHADS	National Center for HIV/AIDS, Dermatology and STDs
YLWH	Youth or young people Living With HIV
OI/ART	Opportunistic Infections/Antiretroviral therapy

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Last (but certainly not least), I thank KHANA Center for Population Health Research in Cambodia, my data collectors, the study sites and my study participants for their contribution and their time.

In the face of an epidemic that puts our science and humanity to test, I hope that I will become all that you have trained me to be and more.

VITA

EDUCATION

Master of Science in Nutrition 2013-2015

National Institute of Public Health-School of Public Health, Phnom Penh, Cambodia

Residency in Pediatrics 2010-2012

Claude Bernard Lyon I University, Lyon, France

Doctor in Pediatrics 2007-2010

University of Health Sciences, Phnom Penh, Cambodia

GRANTS AND CONTRACT AWARDS

Current

UCLA / Cambodia HIV/AIDS training program 2015-present

NIH-FIC Fogarty International Center

University of California, Los Angeles

Total cost: $ 127,534

Completed

NIPH / Cambodia Harvest Organization Scholarship 2013-2015

USAID's Agriculture and Food Security Program via Cambodia Harvest Organization

Total cost: $ 10,000 approximately

Completed

NIPH / FRTP Scholarship 2014-2015

AUSAID via University of New South Wales' Field Research Training Program

Total cost: $ 4,000 approximately

Chapter 1. Introduction and background

In low- and middle-income countries (LMICs), the transition from infectious diseases to non-communicable diseases (NCDs) burdens the health system and calls for effective integration of their care and management (1, 2). In addition, at the present time, many infections (due to advance in treatments) are becoming chronic conditions themselves; and there is no better example than in the case of infection with Human Immunodeficiency Virus (HIV) (2-8). Advances made in the HIV treatments helped people living with HIV (PLWH) survive into older age, therefore, rendering them susceptible to chronic diseases and age-related co-morbidities, as the general population (5, 9-13). Findings from high-income countries (HICs) also suggested that PLWH might be at even higher risk of developing these NCDs than those uninfected due to the HIV infection as well as the antiretroviral therapy (ART) (1, 3, 5-7, 9, 14-20).

However, many LMICs lack epidemiological research on these chronic diseases among PLWH and the complex interaction between HIV-specific factors and NCD traditional risk factors (1, 9, 16, 18, 21, 22). As a result, an assessment of NCD prevalence as well as their risk factors among population that differs by their HIV status is still limited (1, 9). This is also the case for Cambodia. This assessment can help us understand the extent to which the HIV infection and ART contributed to increased risk of NCDs among PLWH and identify those who might be at higher risk of these conditions so that appropriate interventions can be proposed to them in a timely manner.

Without measures taken to properly address these NCDs among PLWH, the efforts put forth in terms of universal ART coverage will end up being wasted (1, 18, 22).

1.1. Epidemiological research on NCDs among PLWH in Cambodia

In 10 years, researchers estimated that deaths from NCDs will surpass those from infectious diseases as their prevalence continue to rise across the globe (10). In Cambodia, according to the World Health Organization (WHO), 64% of total deaths are from NCDs (23). A few years ago, Cambodian researchers, health professionals alike, started making headlines on these so-called slow "silent killers" (24). However, research publications addressing NCDs were still then very limited in the country, representing only about 8% of total publications over the period of more than a decade from 2000 to 2012 (24). In 2010, the Cambodia's Ministry of Health (MOH), in collaboration with the WHO as well as other local and international partnering institutions, launched the first STEPwise Approach to Noncommunicable Disease Risk Factor Surveillance, or in shorts, STEPS or STEP survey, as part of the attempt to describe the burden of NCDs and their risk factors among the Cambodian general population (25, 26). Five years later (2015), the first STEPS survey among PLWH was conducted in Cambodia by KHANA Population Center for Health Research (14, 19). Afterward (in 2016), the STEPS survey among the general population in Cambodia was conducted for the second time by the University of Health Sciences.

It should be noted that each survey described the prevalence of chronic conditions such as diabetes, hypertension and high blood cholesterol, along with their behavioral risk factors, among different study populations. KHANA Population Center for Health Research did a STEP survey among PLWH only, while the 2010 and 2016 STEP surveys were conducted among the general population. Although at a glance, the prevalence of NCDs differs among the two populations, there was no epidemiological study that compares PLWH and the general population in Cambodia.

1.2. Cardiovascular disease (CVD) and their risk assessment among PLWH

NCDs are not created equal. Cardiovascular disease (CVD) accounts for the most deaths each year globally (27) and is the major cause of death among PLWH (28, 29). According to Dr Galea Gauden, the WHO's representative for the People's Republic of China, "The probability of dying between ages 30 and 70 years from the four main NCDs is 18%" (30). In Cambodia, deaths from CVD accounted for 24% of total deaths from NCDs (23).

In the context of HIV, in addition to known behavioral risk factors, HIV-specific factors have been linked with increased risk of CVD either independently or by means of increasing CVD metabolic risk factors (28, 31-37). However, regardless of HIV status, according to the WHO, by eliminating certain behavioral risk factors, we could potentially and significantly reduce both the burden and mortality of CVD (27). This denotes the importance of CVD risk stratification or risk prediction among vulnerable and at risk population in order to identify those who are in need of interventions (34, 38-41). Because CVD risk estimation models takes into account each individual risk profile, it is recommended to be performed regularly after a certain age, depending on the model used (38, 42).

There are several risk prediction models but only one was specifically developed for PLWH, i.e. one that incorporates some HIV-specific factors in their equations (28, 42, 43). However, CVD risk prediction model for PLWH (named the D:A:D model) had not been widely validated and its predictive ability remains somewhat questionable (43-45). Therefore, experts recommend using models which had been developed for the general population such as Framingham Risk Score (FRS) or Atherosclerotic Cardiovascular Disease (ASCVD) score to assess CVD risk among PLWH (43, 45). This recommendation is based on the fact that traditional risk factors (smoking, alcohol consumption and lack of physical activity, for instance) still play significant roles in CVD development, even among those living with HIV (37).

1.3. Young population and NCD risk factors

Despite their young age, young people (adolescents and young adults) are actually prone to adopting many unhealthy lifestyle behaviors, such as smoking and substance abuse, some of which might be contributing to the development of chronic diseases in their late adulthood (46-49). Evidence suggests that these risk behaviors, the majority of which, are associated with overweight/obesity and NCDs, are becoming increasingly common among youth (49). Lack of measures to address and prevent these behaviors among young population now will only exacerbate the problems faced by both the future populations and health care system. In the United States, besides having high prevalence of NCD risk factors, young people aged 16-24 years, were heavily affected by HIV (50). Unfortunately, Cambodia has no official report on this specific young population, neither their HIV nor NCD prevalence rates.

Young people add value to NCD research and have the capacity to shape the future course of NCD epidemic by becoming parts of the prevention strategies (49). This is particularly important at the present time, when many LMICs are or will be going through demographic transition, and urbanization as well as migration patterns are fast becoming a global trend (15, 51). In addition, mounting evidence suggested that rising income levels in LMICs could potentially lead to an increase in the prevalence of NCD risk factors, such as overweight and obesity in the future (51). We can, therefore, reasonably expect to see a rise in prevalence rate of NCDs now or in the near future among our young people including, of course, those living with HIV.

In Cambodia, often times, past studies usually focused on sexual risk behaviors other than those related with NCDs, or they targeted specific groups such as young sex workers or men who have sex with men (MSM) other than young people living with HIV (YLWH) in general

(52-59). Therefore, young population or YLWH in general remain largely understudied and their health needs as well as their risk profile were largely under-addressed.

The health of the future populations depends on that of today's populations, the importance of NCD research among young people could not be overstated.

Thus, in order to halt the future NCD morbidity and mortality in Cambodia, we need to start focusing on young people and their behaviors which carry risk for present or future (chronic) disease development (46). Unlike the young general population, in the context of HIV, YLWH can easily benefit from their regular engagement in care in terms of simple screening or treatment procedures. These simple measures might have a huge impact on their late adult health. Similar to the general population, their risk of chronic diseases could as well be prevented, mainly, through proper and timely course of preventive measures.

Each of the studies I proposed tackled different population subsets in terms of their NCD burden and risk. Both assessments of disease burden and risk contribute to scientific knowledge from LMICs and help inform the future course of public health research priorities and potential resource allocation.

Chapter 2. Study 1: Differences in prevalence and risk factors of non-communicable diseases (NCDs) between people living with HIV (PLWH) and the general population in Cambodia

2.1. Abstract

Objectives: Human Immunodeficiency Virus (HIV) and antiretroviral therapy (ART) had been associated with increased risk of non-communicable diseases (NCDs) such as diabetes and hypertension alongside other well-established traditional risk factors. Empirical evidence from low- and middle-income countries (LMICs) on this relationship are scarce. Therefore, we examined the prevalence of NCDs in people living with HIV (PLWH) and the general population in Cambodia to assess the contribution of HIV and ART on NCDs and identify if locally adapted policies and/or interventions are needed.

Design: Cross-sectional survey.

Methods: We merged data from two surveys conducted among PLWH (n=510) and the general population (n=2747), aged 22 and up, by KHANA Center for Population Health Research (nongovernmental organization) in 2015 and by the University of Health Sciences in 2016, respectively. Both employed a standardized questionnaire and physical/biochemical measurement protocols developed by the World Health Organization (STEPwise Approach to Surveillance or STEP survey or STEPS) and were conducted across selected provinces in Cambodia. We computed NCD prevalence and performed logistic regression to examine the relationship between NCDs and HIV while adjusting for age, sex, residence location, behavioral risk factors (smoking, heavy alcohol consumption, less than 5 servings of fruits and vegetables and low physical activity) and body mass index (BMI).

Results: The prevalence was 9% (n=46) for diabetes, 13% (n=67) for hypertension and 3% (n=16) for high cholesterolemia among PLWH, all of which (except diabetes) were lower than that of the general population. PLWH were more likely to present prediabetes, aOR=7.30 (95% CI: 5.69, 9.36) and diabetes, aOR=1.46 (95% CI: 0.99, 2.17), and less likely to present hypertension and high cholesterolemia, aOR=0.58 (95% CI: 0.42, 0.80) and aOR=0.13 (95% CI: 0.08, 0.23), respectively.

Conclusion: High prevalence of prediabetes and diabetes among PLWH underscores the need to put in place proper treatment and screening measures to address these conditions among this population.

2.2. Introduction

The increase in the coverage of antiretroviral therapy (ART) is marked with an increase in life expectancies of people living with Human Immunodeficiency Virus or HIV (PLWH) and, to various extent, in other age-related co-morbidities and non-communicable diseases or NCDs (7, 14, 19, 60-62). The infection, the virus and the treatments might act independently and/or by influencing known traditional risk factors for NCDs (33, 63). As a result, NCD risk might be higher among PLWH and this had been reported in many studies conducted in HICs (11, 12, 64, 65). Their increased NCD risk could be due to prolonged ART use and certain ART regimen (45, 66-68), but it also depends on whether or not they present with other known traditional risk factors of these NCDs, as in the case of the general population (69).

However, country-specific epidemiological data is still lacking in many low-middle-income countries (LMICs) (16, 18, 21). This data is important because differences in the distribution of NCD traditional and HIV-specific risk factors across country settings raised concerns on whether findings from HICs could also be applicable to other settings (5, 16, 18, 21, 65).

Cambodia is home to roughly 16 million people (70). Approximately 65,000 were estimated to be living with HIV and the ART coverage was about 80% as of 2016 estimate (71). The country underwent a demographic and epidemiological transition since 2000 as NCD mortality overtook that of infectious diseases (24). Despite this, the transition of public health research focus from infections to NCDs has been slow, resulting in very few research studies addressing NCDs over the years (24).

Therefore, we examined the relationship of these NCDs and HIV by comparing the prevalence of NCDs among the general population with that of PLWH in Cambodia. Our study will help identify whether PLWH in Cambodia are at increased risk of certain conditions that merit early or regular screening as well as other types of interventions.

2.3. Methods

Information on the general population and those who are living with HIV was obtained by merging STEP[1] surveys conducted by the University of Health Sciences (UHS) in 2016 and by KHANA Center for Population Health Research in 2015, respectively. Both surveys had > 90% response rates and included information on socio-demographics, behavioral risk factors, and measurements of blood pressure, total cholesterol, and glucose levels. Blood pressure was measured three times, five minutes apart, and the average was used for high blood pressure classification. Both glucose and cholesterol levels were measured in the morning before breakfast and after fasting the night before. Physical activity (recreation- or work-related) included locally-adapted activities, such as farming and household chores. Body Mass Index (BMI) classification was based on Asian-specific cutoffs.

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[1] The World Health Organization (WHO) 's standardized questionnaire and measurement protocols called the STEPwise approach to NCD risk factor surveillance - STEP survey or STEPS.

We used a subset of the UHS's survey pertaining only participants aged 22 and above (n=2747) to match that of KHANA's study population (n=510). The details of the KHANA's STEP survey were described elsewhere (14). It should be noted that, while KHANA conducted their survey at designated HIV clinics across 4 provinces and the capital city, UHS was a national household survey. The data collectors for both surveys were a mixture of medical (mostly nurses) and non-medical personnel; they all had undergone appropriate training with human subjects certified trainers of their corresponding institutions.

Definition and classification (72-76)

Definition and classification of variables are as follow: **1)** smokers refer current (daily or not) users of any tobacco products. **2)** heavy drinkers refer to those who had, during the past week: 4 standard drinks[2] or more on any one occasion or 14 standard drinks or more in total (men), or 3 standard drinks or more on any one occasion or 7 standard drinks or more in total (women). **3)** fruit and vegetable consumption refer to any one-day consumption on a typical week within the past year. **4)** low physical activity refers to less than 75 minutes of work or recreation activity of vigorous intensity per week or less than 150 minutes of recreation activity of moderate intensity per week. **5)** nutritional status – underweight refers to BMI < 18.5, normal weight refers to BMI between 18.5 and 23, overweight and obese refers to BMI ≥ 23 and BMI ≥ 25, respectively. **6)** Hypertension: mean systolic blood pressure (SBP) ≥ 140 mmHg and/or mean diastolic blood pressure ≥ 90 mmHg (DBP) and/or on anti-hypertensive drugs. **7)** Diabetes: fasting glucose ≥ 126 mg/dL and/or on anti-diabetic drugs. **8)** Prediabetes: fasting glucose between 101-125 mg/dL. **9)** Prehypertension: mean SBP between 120-139 mmHg and/or mean

[2] A standard drink is defined as one with a net content of approximately 10g of pure ethanol (in accordance with the WHO's STEP survey showcards' contents).

DBP between 80-89 mmHg. **10)** High cholesterolemia: total cholesterol between ≥ 240 mg/dL and/or on cholesterol lowering drugs. **11)** Borderline- high cholesterolemia: total cholesterol between 200-239 mg/dL.

Power calculation and statistical analysis

The present study (N=3257) has more than 90% power to detect differences in the prevalence of prediabetes, hypertension, high and borderline-high cholesterolemia.

We calculated the prevalence of hypertension, prehypertension, diabetes, prediabetes, high and borderline-high cholesterolemia among PLWH and the general population. We fitted a separate logistic regression model to examine the association between each of these conditions and HIV, reporting the crude and adjusted odds ratios (ORs), controlling for confounders including age, sex, residence location (Phnom Penh vs. provinces), behavioral risk factors (smoking, heavy drinking, less than 5 servings of fruits and vegetables, low physical activity) and BMI. All analyses were performed using STATA 14 (Copyright 1985-2015 StataCorp LLC).

Ethical considerations

The current study was approved by the Institutional Review Board of the University of California Los Angeles (UCLA IRB#18-001789) in 2018 and the National Ethics Committee for Health Research in Cambodia (NECHR #010) in 2019. All study volunteers provided verbal and written consents and understood that no identifying information or blood sample had been collected or stored.

2.4. Results

Socio-demographics

Findings on socio-demographic and other characteristics are described in details in **Table 2-1**. We had a total of 3257 study volunteers, aged between 22-78 years. The only similarities between the two groups were in terms of their mean age and gender distribution. The mean age was around 44 years (SD=8) and 45 years (SD=13) for the general population group and PLWH, respectively. Female participants accounted for about two-thirds in each group.

Other characteristics (education, occupation and marital status) were quite distinct (likely related to differences in their residence location). PLWH were more likely than the general population to have had at least primary education (49% (n=249) vs. 21% (n=577)), but the percentage of those who reported having completed high school or higher were comparable among these two groups (approximately 5%). The majority of participants from both groups were either salary- or self-employed (which includes farmers). These two employment statuses accounted for 75% (n=385) of PLWH and 85% (n=2333) of the general population. Over two-thirds of participants from both groups were from provinces, although this was much more significant among the general population, 95% (n=2607), than PLWH, 74% (n=378).

Prevalence of behavioral risk factors and NCDs

Heavy alcohol consumption was more common among the general population, 22% (n=212), than PLWH, 8% (n=18), while smoking was similar between the two groups (15% or n=75 for PLWH and n=429 for the general population). Low physical activity, on the other hand, was more prevalent among PLWH, 31% (n=98), than the general population, 17% (n=222). Overweight and obesity was higher in the general population group (41% (n=1102) vs. 22% (n=113) in PLWH).

Half of PLWH (n=255) had prediabetes compared with only 16% (n=374) of the general population, while diabetes differed only slightly among them **(Table 2.1)**. Although high cholesterolemia was rather prevalent among the general population (20% (n=517)), its prevalence was only 3% (n=16) among PLWH. Similarly, hypertension was 22% (n=600) and

13% (n=67) among the general population and PLWH, respectively. More details on these conditions, their risk factors and other socio-demographics are in **Table 2-1**.

We also noted higher percentage of smoking and heavy alcohol use among male than female participants, although more female participants had low physical activity and high BMI **(Figure 2-1)**.

HIV-specific factors and NCDs

We presented in **Table 2.2** the distribution of some HIV-specific factors by NCD status. The majority of our PLWH had been behaviorally infected and the average duration of HIV duration was about 10 years. There appeared to be no association between any of the HIV-specific factors and NCDs, except for hypertension and prehypertension (with high CD4 cell count measured within the last 6 months), and for high and borderline-high cholesterolemia (with being behaviorally infected and duration of HIV infection) **(Table 2.2)**.

Associations between NCDs and HIV

We reported in **Table 2-3** the results from logistic regression models that examined the effect of HIV on glucose status. We found that PLWH appeared to be at higher odds of prediabetes, aOR=7.30 (95% CI: 5.69, 9.36) and, to a lesser extent, diabetes, aOR=1.46 (95% CI: 0.99, 2.17). Additionally, we showed the relationship between fasting glucose levels and HIV status, stratified by BMI (**Figures 2-2**) and by sex (**Figure 2-3)**. PLWH always had higher fasting glucose levels regardless of their BMI status and sex.

On the contrary, PLWH were much less likely than the general population to present hypertension, aOR=0.58 (95%CI: 0.42, 0.80) **(Table 2-4)**, and high cholesterolemia, with aOR=0.13 (95% CI: 0.08, 0.23) **(Table 2-5)**. Similarly, we observed lower odds of prehypertension **(Table 2-4)** and borderline-high cholesterolemia **(Table 2-5)** among PLWH.

2.5. Discussion

We found higher prevalence of prediabetes and diabetes and lower prevalence of hypertension and high cholesterolemia among PLWH, compared with the general population. Although the roles of HIV infection and ART had been implicated in the pathophysiological pathways of certain metabolic disorders among PLWH (33, 77), findings across different studies had been inconsistent.

Diabetes and prediabetes

A diabetes incidence rate of 10% among HIV-infected individuals (compared with 3% among those uninfected) had been reported by the Multicenter Aids Cohort Study (MACS) over 4 years of follow-up (78). A 6-year incidence rate of 7% was reported from a study based on data from the TREAT Asia HIV Observational Database (TAHOD), but much lower rates had been reported in other cohorts including the Swiss HIV Cohort, and the D:A:D study (66). Similarly, A systematic review and meta-analysis of over 40 articles on glucose metabolism status among PLWH reported overall cumulative incidence of approximately 5% (values range from 3-13%) for diabetes and 15% for prediabetes (values range from 0-50%) (79). However, of all these reported numbers excluded prevalent cases, which might partially explain why most of their rates were slightly lower compared to ours.

Based on the data from 3 large HIV clinics in London, the prevalence was 15% and 17% for diabetes and prediabetes, respectively; and PLWH appeared to be at higher risk of diabetes (2-fold) compared with the general population (80, 81). Higher diabetes prevalence in their study could have been due to the different age and demographic constitution of their study population compared to ours: their median age was older (49 years), their clients were mostly Caucasian, followed by Black African and Black Caribbean, and more than 70% were male (80, 81). On the contrary, HIV did not appear to increase diabetes risk in the Danish cohort, but this cohort was predominantly white and younger than ours as well (81, 82).

Nevertheless, our diabetes prevalence was comparable with a study that utilized National Health Nutrition Examination Survey (NHANES) and Medical Monitoring Project (MMP) and another study in Iran (83, 84). The first one reported the prevalence of diabetes at 8% and 10% in the general population and in PLWH, respectively (83). The second study (Iran) found that 6% and 50% of their study population had diabetes and prediabetes, respectively (84). There were also other studies that reported a high prevalence of prediabetes (> 30%) among PLWH (78, 85), affirming that prediabetes can be very common among this population, as demonstrated in our findings. Additionally, similar to our results shown in **Table 2-1**, one Chinese study reported higher mean glucose levels in PLWH than those uninfected, but their sample consisted of only men (85).

To sum up, these seemingly quite different figures reported from various studies could be the result of many factors. First, it has been established that along with BMI, age, sex and race/ethnicity, HIV infection and ART regimen also have influences on glucose (Nucleoside Reverse Transcriptase Inhibitors "NRTIs" in particular) and lipid metabolism (66, 79, 81, 86), therefore, fluctuations in the prevalence or incidence rates across these different studies could very well be the reflection of differences in the distribution of traditional risk factors and HIV-specific factors among the study populations. In our sample of PLWH, 78% were on combination therapy (NRTTs and Non-Nucleoside Reverse Transcriptase Inhibitors "NNRTIs") and 42% of them were on Zidovudine (result not shown). Zidovudine is a type of NRTIs that has been linked with significant risk of diabetes (86, 87).

Second, the reporting of incidence or prevalence rates also made it challenging to directly compare across studies.

Lastly, the definitions of diabetes and prediabetes used were not always consistent across studies. Although, the majority of studies would use a standard definition of fasting glucose above 126 mg/dL to determine the diabetes status and/or self-report diabetes status (78), others might use glycate hemoglobin (HbA1C), the oral glucose tolerance test with or without self-reported diabetes status (66, 80, 83). Discrepancies in each test's sensitivity and specificity functions could potentially result in discrepancies in these reported figures.

Hypertension and high cholesterolemia

Our findings on hypertension was comparable to the Polish study which reported higher incidence rate of hypertension among the general population (33%) than PLWH (28%) (88), and to some other cross-sectional studies conducted in China and India (85, 89). In addition, lower mean systolic and diastolic blood pressure as well as lower hypertension prevalence among PLWH (compared with those uninfected) had also been published in a 2015 review article (69). However, other meta-analyses reported a higher prevalence of hypertension among PLWH compared with those uninfected (68, 90). Although we should note that both of these meta-analyses included significantly more studies from HICs than LMICs and it was not clear if each study included in the analyses classified those on anti-hypertensive medications as hypertensive as we did in our study.

Our findings on total cholesterolemia were similar to some other Asian observational studies reported in a 2017 systematic review on cardiovascular disease risk (85). Mean total cholesterolemia had been found to be lower in PLWH compared to those uninfected in two cross-sectional studies, one conducted in South Korea and another one in China (85, 91), and in one case-control study in China (85).

Lower prevalence of hypertension and high cholesterolemia among PLWH in our study could be due to multiple reasons. First, we showed that traditional risk factors for hypertension and high total cholesterol, such as smoking, heavy drinking and overweight/obesity, were less common among our PLWH participants, who, due possibly to their regular interaction with health care workers, were probably more health conscious. Second, the ART usually linked with dyslipidemia is PIs (37, 45), a regimen that is taken by only 3% of PLWH in our sample. Third, low prevalence of hypertension among PLWH might also explain a low prevalence of high blood cholesterol because the latter had been known to also increase risk of hypertension (67). The general population had higher prevalence of cholesterolemia, as a result, they also had higher prevalence of hypertension. Lastly, our general population group came from a household STEP survey, it might have been the case that the survey selectively captured a lot more population who were not healthy and, therefore, more likely to be home.

Limitations

We also reckon several limitations of our study. First, we took careful interpretations derived from any associations between HIV and NCDs, suggested by these survey data. We have no means of knowing for sure if these conditions actually occurred after HIV infection for our participants who are living with HIV. Nevertheless, on average, PLWH in our study sample had been living with the infection for almost 10 years, and given their average age (around 44 years), it is highly unlikely that our PLWH had had these conditions before the onset of HIV infection, as the prevalence of chronic diseases among younger population in Cambodia was quite low in the past (based on the 2010 STEPS report) (26).

Second, because we were not able to ascertain the HIV status for our participants in the general population, misclassification might have occurred. However, the prevalence of HIV among the general population is less than 1% in Cambodia, the amount of misclassification, if there is any, seems to be too small to alter any associations we observed.

Lastly, there were several covariates related to the NCDs that were not measured in the original surveys, which includes oral contraceptive use (for women) and birth history (prematurity or low birth weight). As a result, we could not account for any of these factors in the analysis. Nevertheless, the focus of the STEP survey is the modifiable lifestyle factors, many of which were included in our regression model.

Conclusion

High prevalence of prediabetes and diabetes among PLWH in Cambodia compared with the general population raises questions and concerns over early and regular screening measures and future management for the HIV-diabetes co-existence. In addition, the Cambodia's HIV treatment guidelines might need to be further investigated as 70% of children living with HIV under the age of 15 had Zidovudine in their ART regimen[3], a type of NRTI known to increase diabetes risk. Future studies should examine why there were significant differences in the distribution of some HIV-specific factors among those with certain NCDs (high blood pressure and elevated total cholesterol) but not others (diabetes and prediabetes).

Regardless of HIV status, many of these conditions could be lessened to a great extent with timely lifestyle interventions as well as easily available medications. Without proper treatment or screening measures to address prediabetes, diabetes is inevitable. Moreover, without

[3] Annual Report 2016. MOH/NCHADS. Cambodia. 2016.

reinforcing screening recommendations and lifestyle education among this vulnerable population, the future burden of these conditions and other NCDs, such as cardiovascular disease will have huge economical and logistical effects on our resource-restrained health care system.

2.6. Tables and figures

Table 2-1. Key characteristics of study participants, STEPS, Cambodia, 2015/2016.

Characteristics	**PLWH (n=510)**		**General population (n=2747)**	
Socio-demographics	n	%	n	%
Gender				
Male	170	33.3	884	32.2
Female	340	66.7	1863	67.8
Age (mean, SD)	(44.8, 12.7)		(44.3, 8.4)	
22-34	43	8.4	742	27.0
35-44	212	41.6	663	24.1
45-55	191	37.5	643	23.4
55+	63	12.4	699	25.5
Education				
None or less than primary	115	22.6	1713	62.4
Completed primary	249	48.8	577	21.0
Completed secondary	121	23.7	312	11.4
Completed high school or higher	25	4.9	144	5.2
Occupation				
Salary employed	155	30.4	257	9.4
Self-employed	230	45.1	2076	75.6
Unemployed	125	24.5	414	15.1
Marital status				
Single	8	1.6	130	4.7
Married+cohabiting	314	61.7	2175	79.2
Separated	6	1.2	62	2.3
Divorced	39	7.7	62	2.3
Widowed	142	27.9	318	11.6
Residence location				
Province	378	74.1	2607	94.9
Phnom Penh	132	25.9	140	5.1
NCD risk factors				
Smokers	75	14.7	429	15.6
Heavy drinkers	18	8.5	212	22.3
< 5 servings of fruits and vegetables	466	91.5	1446	53.0
Low physical activity	98	30.9	222	17.0
Body Mass Index (BMI)				
Normal weight	297	58.3	1217	45.5
Underweight	99	19.5	355	13.3
Overweight and obese	113	22.2	1102	41.2

Table 2-1. Key characteristics of study participants, STEPS, Cambodia, 2015/2016. (continued)

Characteristics	PLWH (n=510)		General population (n=2747)	
NCDs	n	%	n	%
Blood glucose				
Prediabetes	255	55.2	374	16.1
Diabetes	46	9.1	185	7.4
Fasting blood glucose† (mean, SD)	(106.3, 24.0)		(94.0, 31.3)	
Blood pressure				
Prehypertension	148	33.5	810	38.0
Hypertension	67	13.2	600	22.0
SBP† (mean, SD)	(117.9, 16.2)		(119.7, 18.1)	
DBP† (mean, SD)	(73.8, 10.2)		(78.6, 11.7)	
Total cholesterol				
Borderline-high	93	18.9	671	32.3
High	16	3.2	517	19.9
Fasting total cholesterol† (mean, SD)	(180.3, 30.7)		(198.8, 50.6)	
Currently on treatment				
High blood pressure	22	4.3	172	6.3
Diabetes	1	0.2	59	2.2
High total cholesterol	2	0.4	18	0.7

SD, Standard Deviation.
† Excluded those currently on treatment for each specified condition.

Table 2-2. Distribution of HIV-specific factors by NCD status, STEPS, Cambodia, 2015/2016.

HIV-specific factors	Diabetes and prediabetes	Hypertension and prehypertension	High and borderline-high cholesterolemia
	n (%)	n (%)	n (%)
On ART 24 months or longer	281 (95.3)	201 (96.6)	104 (98.1)
> 350 CD4 cell count	178 (69.0)	111 (61.3)*	67 (72.0)
NRTI and NNRTI (vs. regimen with PI)	271 (96.8)	196 (97.0)	96 (96.0)
Behaviorally infected (vs. perinatally)	299 (99.3)	212 (98.6)	106 (97.3)*
Living with HIV ≥ 60 months	259 (86.1)	186 (86.5)	100 (91.7)
Duration of HIV infection (mean, SD)	9.8 (4.7)	9.6 (4.6)	10.7 (4.9)*

NRTI, Nucleoside Reverse Transcriptase Inhibitor.
NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor.
PI, Protease Inhibitor.
* P-value ≤ 0.05.

Table 2-3. Association between diabetes and prediabetes and HIV, STEPS, Cambodia, 2015/2016.

	Diabetes		Prediabetes	
Predictors	Crude OR (95% CI)	Adjusted OR† (95% CI)	Crude OR (95% CI)	Adjusted OR† (95% CI)
HIV+ (ref. general population)	1.30 (0.93, 1.82)	1.46 (0.99, 2.17)	6.73 (5.44, 8.34)	7.30 (5.69, 9.36)
Female (ref. male)	1.05 (0.79, 1.40)	1.01 (0.74, 1.39)	0.91 (0.76, 1.10)	0.94 (0.76, 1.17)
Age (ref. 22-34)				
35-44	2.47 (1.30, 4.69)	2.32 (1.16, 4.64)	2.73 (2.04, 3.64)	1.59 (1.16, 2.17)
45-54	5.98 (3.30, 10.86)	5.83 (3.05, 11.12)	3.39 (2.53, 4.52)	2.13 (1.56, 2.89)
55+	8.91 (4.95, 16.01)	9.57 (5.07, 18.06)	2.86 (2.12, 3.87)	2.64 (1.93, 3.61)
Currently living in Phnom Penh (ref. in provinces)	2.49 (1.72, 3.61)	1.88 (1.24, 2.83)	2.51 (1.88, 3.35)	1.02 (0.73, 1.42)
2 or more behavioral risk factors‡	0.97 (0.68, 1.37)	0.89 (0.61, 1.31)	1.49 (1.20, 1.84)	1.04 (0.80, 1.34)
BMI (ref. normal weight)				
Underweight	0.67 (0.39, 1.16)	0.56 (0.32, 0.98)	0.98 (0.75, 1.28)	0.87 (0.65, 1.17)
Overweight and obese	2.39 (1.79, 3.20)	2.33 (1.72, 3.16)	1.24 (1.04, 1.50)	1.69 (1.36, 2.10)

CI, Confidence interval.
Diabetes: fasting glucose ≥ 126 mg/dL and/or on anti-diabetic drugs.
Prediabetes: fasting glucose between 101-125 mg/dL.
† Adjusted for sex, age, residence location, behavioral risk factors and BMI.
‡ Behavioral risk factors include smoking, heavy alcohol consumption, less than 5 servings of fruit and vegetable consumption and low physical activity.

Table 2-4. Association between hypertension and prehypertension and HIV, STEPS, Cambodia, 2015/2016.

	Hypertension		**Prehypertension**	
Predictors	**Crude OR (95% CI)**	**Adjusted OR† (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR† (95% CI)**
HIV+ (ref. general population)	0.54 (0.41, 0.71)	0.58 (0.42, 0.80)	0.82 (0.66, 1.02)	0.77 (0.58, 1.00)
Blood glucose (ref. normal)				
Prediabetes	1.44 (1.16,1.79)	1.30 (1.02, 1.67)	1.37 (1.12, 1.68)	1.26 (1.00, 1.58)
Diabetes	3.83 (2.89, 5.08)	2.16 (1.58, 2.96)	1.87 (1.31, 2.68)	1.37 (0.93, 2.02)
Blood cholesterol (ref. normal)				
Borderline-high	1.56 (1.26, 1.92)	1.19 (0.95, 1.50)	1.20 (0.99, 1.47)	1.06 (0.85, 1.31)
High	2.62 (2.11, 3.27)	1.50 (1.16, 1.94)	1.90 (1.51, 2.40)	1.67 (1.28, 2.19)
Female (ref. male)	0.79 (0.66, 0.95)	0.75 (0.60, 0.93)	0.64 (0.54, 0.76)	0.65 (0.53, 0.79)
Age (ref. 22-34)				
35-44	2.37 (1.70, 3.29)	2.27 (1.58, 3.25)	1.80 (1.44, 2.26)	1.75 (1.36, 2.25)
45-54	4.41 (3.21, 6.05)	4.03 (2.84, 5.72)	2.20 (1.75, 2.77)	2.09 (1.61, 2.70)
55+	7.33 (5.36, 10.01)	6.04 (4.26, 8.57)	2.46 (1.93, 3.14)	2.35 (1.78, 3.09)
Currently living in Phnom Penh (ref. in provinces)	1.22 (0.91, 1.64)	1.01 (0.71, 1.44)	1.15 (0.86, 1.54)	0.98 (0.70, 1.37)
2 or more behavioral risk factors‡	1.26 (1.02, 1.56)	1.25 (0.97, 1.60)	1.34 (1.09,1.64)	1.19 (0.94, 1.52)
BMI (ref. normal weight)				
Underweight	0.70 (0.51, 0.98)	0.65 (0.46, 0.92)	0.64 (0.50, 0.83)	0.64 (0.48, 0.83)
Overweight and obese	2.74 (2.28, 3.30)	2.45 (2.00, 3.02)	1.85 (1.54, 2.21)	1.80 (1.48, 2.19)

CI, Confidence Interval.

Hypertension: mean SBP ≥ 140 mmHg and/or mean DBP ≥ 90 mmHg and/or on anti-hypertensive drugs.

Prehypertension: mean SBP between 120-139 mmHg and/or mean DBP between 80-89 mmHg.

† Adjusted for diabetes status, blood cholesterol status, sex, age, residence location, behavioral risk factors and BMI.

‡ Behavioral risk factors include smoking, heavy alcohol consumption, less than 5 servings of fruit and vegetable consumption and low physical activity.

Table 2-5. Association between high and borderline-high cholesterolemia and HIV, STEPS, Cambodia, 2015/2016.

	High cholesterolemia		Borderline-high cholesterolemia	
Predictors	**Crude OR (95% CI)**	**Adjusted OR† (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR† (95% CI)**
HIV+ (ref. general population)	0.13 (0.08, 0.22)	0.13 (0.08, 0.23)	0.49 (0.38, 0.62)	0.46 (0.35, 0.61)
Female (ref. male)	2.46 (1.94, 3.11)	2.41 (1.86, 3.13)	1.54 (1.28, 1.85)	1.57 (1.28, 1.92)
Age (ref. 22-34)				
35-44	0.96 (0.70, 1.33)	1.44 (1.00, 2.07)	1.09 (0.86, 1.39)	1.23 (0.95, 1.59)
45-54	1.91 (1.42, 2.56)	3.18 (2.27, 4.45)	1.51 (1.18, 1.92)	1.87 (1.45, 2.42)
55+	3.51 (2.64, 4.66)	5.18 (3.75, 7.17)	1.92 (1.49, 2.47)	2.20 (1.69, 2.86)
Currently living in Phnom Penh (ref. in provinces)	1.13 (0.81, 1.57)	1.68 (1.15, 2.46)	1.17 (0.86, 1.58)	1.47 (1.05, 2.06)
2 or more behavioral risk factors‡	0.58 (0.44, 0.76)	0.96 (0.71, 1.31)	0.70 (0.56, 0.87)	0.88 (0.69, 1.13)
BMI (ref. normal weight)				
Underweight	0.77 (0.55, 1.08)	0.59 (0.41, 0.84)	0.69 (0.52, 0.91)	0.60 (0.45, 0.80)
Overweight and obese	1.90 (1.55, 2.33)	1.48 (1.19, 1.84)	1.54 (1.28, 1.84)	1.33 (1.09, 1.60)

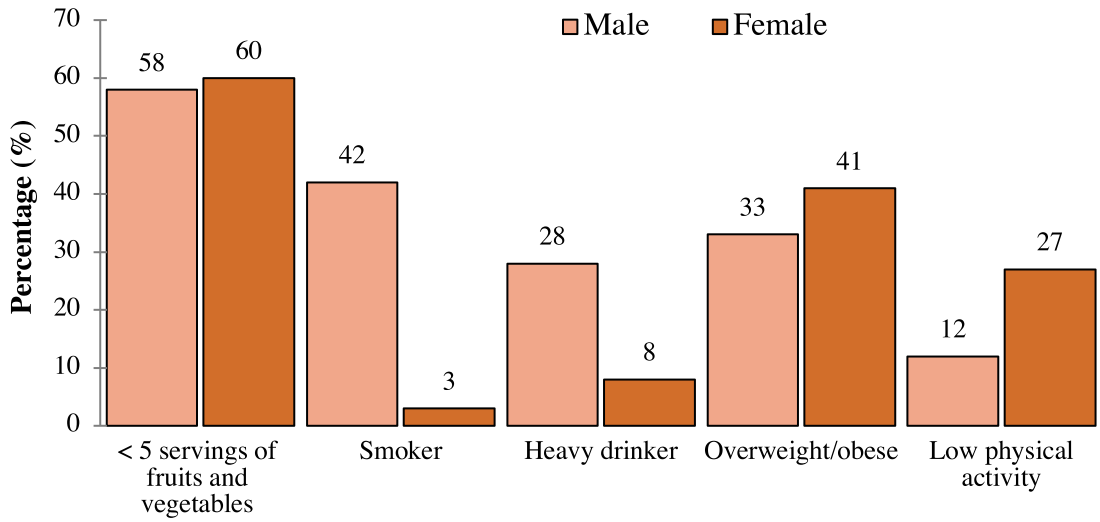
CI, Confidence Interval.

High cholesterolemia: total cholesterol between ≥ 240 g/dL and/or on cholesterol lowering drugs.

Borderline-high cholesterolemia: total cholesterol between 200-239 g/dL.

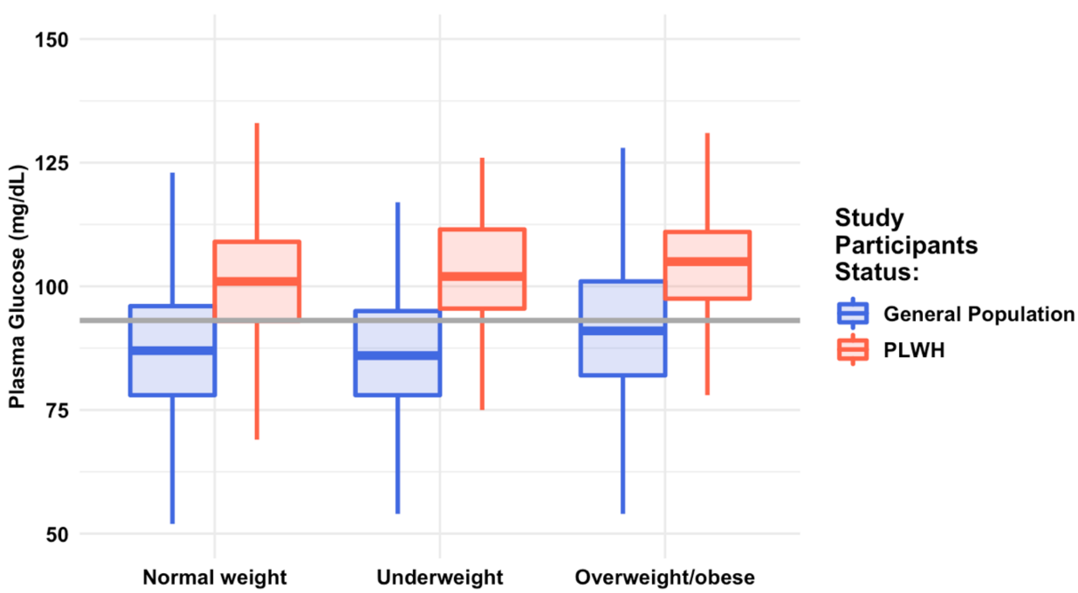
† Adjusted for sex, age, residence location, behavioral risk factors and BMI.

‡ Behavioral risk factors include smoking, heavy alcohol consumption, less than 5 servings of fruit and vegetable consumption and l ow physical activity.



Source: Data from the 2016 UHS (n=2747) and 2015 KHANA (n=510) STEP surveys, Cambodia

Figure 2-1. Distribution of NCD risk factors among study participants by sex.



Source: 2016 UHS (n=2747) and 2015 KHANA (n=510) STEP surveys, Cambodia

Figure 2-2. Association between fasting glucose levels and HIV, stratified by BMI.

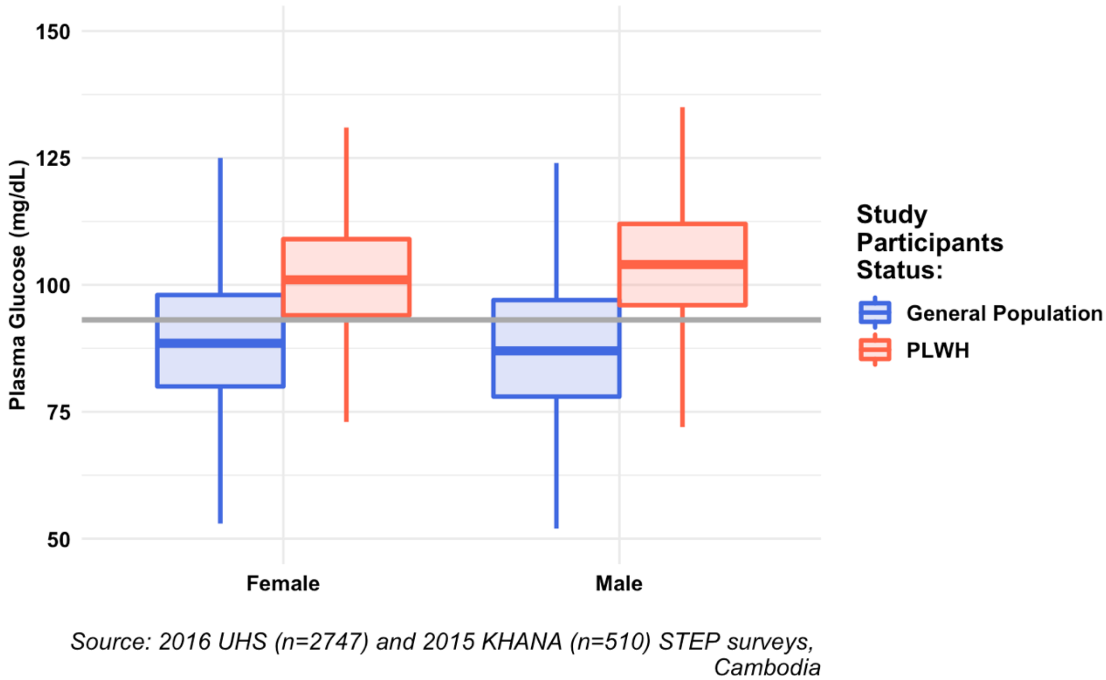


Figure 2-3. Association between fasting glucose levels and HIV, stratified by sex.

Chapter 3. Study 2: 10-year cardiovascular disease (CVD) risk estimation of people living with HIV (PLWH) compared with that of the general population in Cambodia

3.1. Abstract

Objectives: Cardiovascular Disease (CVD) risk stratification is an important first step to informing clinical decisions and preventive efforts for CVD, but rarely assessed in Cambodia. Using the Framingham Risk Score (FRS), therefore, we estimated 10-year CVD risk among the general population and people living with Human Immunodeficiency Virus or HIV (PLWH) to help identify subgroups who should be targeted for CVD prevention.

Design: Cross-sectional survey.

Methods: We merged data from two surveys conducted among PLWH (n=499) and the general population (n=2383), aged 30 and above, by KHANA Center for Population Health Research (nongovernmental organization) in 2015 and by the University of Health Sciences in 2016, respectively. Both employed a standardized questionnaire and physical/biochemical measurement protocols developed by the World Health Organization (STEPwise Approach to Surveillance or STEP survey or STEPS) and were conducted across selected provinces in Cambodia. We computed FRS for each individual and performed logistic regression to examine the relationship between moderate-to-high 10-year CVD risk and HIV, while adjusting for age, sex, residence location, behavioral risk factors and body mass index (BMI).

Results: We found 18% (n=91) of PLWH and 26% (n=615) of the general population were at moderate to high 10-year CVD risk (FRS ≥ 10%). In logistic regression, the odds of moderate-to-high 10-year CVD were about the same between PLWH and the general population, aOR=0.88 (95% CI: 0.60, 1.29).

Conclusion: Although PWLH in Cambodia were as likely as the general population to develop future CVD, early lifestyle modifications and/or medical intervention targeting them could be one of the most cost-effective strategies for future CVD prevention given their regular contact with care.

3.2. Introduction

Deaths from cardiovascular disease (CVD) accounted for the majority of mortality in both the general population and people living with Human Immunodeficiency Virus or HIV (PLWH) (28, 29). In the context of HIV infection, several HIV-related factors, such as antiretroviral therapy (ART) and the HIV virus were hypothesized to directly increase the risk of CVD or alter the traditional CVD risk factor profile among this population, rendering them, therefore, more susceptible to develop atherosclerosis and other cardiovascular anomaly (45, 92). Multiple risk assessment platforms are available and recommended for use to estimate the 10-year CVD risk among the general population, but only one was developed specifically for PLWH (28, 42, 43).

More general 10-year CVD risk estimation models including the Framingham Risk Score (FRS) or the Atherosclerotic Cardiovascular Disease score (ASCVD) were generally recommended by experts for regular CVD risk assessment among PLWH (34, 43, 45). For this population, especially, in the era of ART, the importance of CVD risk assessment cannot be overlooked.

Being able to stratify subgroups of population according to their CVD estimated risk can help guide clinical management and intervention efforts, and, therefore, is an essential step to CVD prevention (34, 93). However, most CVD assessment studies pertaining to HIV populations were from high-income countries (HICs) (85).

In Cambodia, CVD accounted for about one-third of total deaths from NCDs, but the World Health Organization estimated that CVD risk assessment might be offered in less than 25% of the population at primary healthcare providers. (23).

Therefore, using the FRS, the proposed study aims to assess the 10-year CVD risk among the general population and those who are living with HIV in Cambodia in order to help identify those who might be at higher risk of future CVD events. This assessment could help inform lifestyle and/or medical interventions that should be proposed as well as the population that should be targeted.

3.3. Methods

We merged STEP[4] surveys conducted by the University of Health Sciences (UHS) in 2016 (n=2383) and by KHANA Center for Population Health Research in 2015 (n=499), respectively, among those aged 30 and above. Both surveys had > 90% response rates and included information on socio-demographics, behavioral risk factors, and measurements of blood pressure, total cholesterol, and glucose levels. Blood pressure was measured three times, five minutes apart, and the average was used for high blood pressure classification. Both glucose and total cholesterol levels were measured in the morning before breakfast and after fasting the night before. Physical activity (recreation- or work-related) included locally-adapted activities, such as farming and household chores. Body Mass Index (BMI) classification was based on Asian-specific cutoffs.

The details of the KHANA's STEP survey were described elsewhere (14). It should be noted that, while KHANA conducted their survey at designated HIV clinics across 4 provinces

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[4] The World Health Organization (WHO) 's standardized questionnaire and measurement protocols called the STEPwise approach to NCD risk factor surveillance - STEP survey or STEPS.

and the capital city, UHS STEP survey was a national household survey. The data collectors for both surveys were a mixture of medical (mostly nurses) and non-medical personnel and had undergone appropriate training with human subjects certified trainers of their corresponding institutions.

Regarding the Framingham Risk Score, the calculation was based on the equations available on the Framingham study website (https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/). The conventional Framingham risk prediction models include age, sex, systolic blood pressure, diabetes status, smoking status, hypertension treatment status and BMI (94).

Definition and classification (72-76)

Definition and classification of variables are as follow: **1)** smokers refer to current (daily or not) users of any tobacco products. **2)** heavy drinkers refer to those who had, during the past week: 4 standard drinks[5] or more on any one occasion or 14 standard drinks or more in total (men), or 3 standard drinks or more on any one occasion or 7 standard drinks or more in total (women). **3)** fruit and vegetable consumption refer to any one-day consumption on a typical week within the past year. **4)** low physical activity refers to less than 75 minutes of work or recreation activity of vigorous intensity per week or less than 150 minutes of recreation activity of moderate intensity per week. **5)** nutritional status – underweight refers to BMI < 18.5, normal weight refers to BMI between 18.5 and 23, overweight and obese refers to BMI ≥ 23 and BMI ≥ 25, respectively. **6)** Hypertension: mean systolic blood pressure (SBP) ≥ 140 mmHg and/or mean diastolic blood pressure (DBP) ≥ 90 mmHg and/or on anti-hypertensive drugs. **7)** Diabetes:

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[5] A standard drink is defined as one with a net content of approximately 10g of pure ethanol (in accordance with the WHO's STEP survey showcards' contents).

fasting glucose ≥ 126 mg/dL and/or on anti-diabetic drugs. **8)** Prediabetes: fasting glucose between 101-125 mg/dL. **9)** Prehypertension: mean SBP between 120-139 mmHg and/or mean DBP between 80-89 mmHg. **10)** High cholesterolemia: total cholesterol between ≥ 240 mg/dL and/or on cholesterol lowering drugs. **11)** Borderline-high cholesterolemia: total cholesterol between 200-239 mg/dL. **12) 10-year CVD risk: Low** – FRS < 10%, **moderate** – FRS between 10-20% and **high** – FRS > 20%.

Power calculation and statistical analysis

With the total sample size of 2882, the present study has 92% power to detect a difference in proportion of moderate-to-high 10-year CVD risk between the two groups.

We calculated the for each individual the FRS using the equations provided on the Framingham heart study website[6] and categorized them as low (FRS < 10%), moderate (FRS between 10-20%) and high (FRS > 20%) 10-year CVD risk. It should be noted that the FRS can only be calculated for subjects aged 30 years or older and with systolic blood pressure (SBP) of 90 mmHg at the minimum. We, therefore, replaced those with SBP less than 90 mmHg with 90 mmHg as value for their SBP (n=36).

We also calculated percentages and means for other categorical and continuous variables, respectively, by their FRS category. Logistic regression was performed to examine the association between moderate to high 10-year CVD risk (i.e. FRS ≥ 10%) and HIV. We reported both the crude and adjusted odds ratios (ORs), controlling for other covariates including age, sex, residence location (Phnom Penh or provinces), behavioral risk factors (smoking, heavy drinking,

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[6] https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/

less than 5 servings of fruits and vegetables, low physical activity) and BMI. All analyses were performed using STATA 14 (Copyright 1985-2015 StataCorp LLC).

Ethical considerations

The current study was approved by the Institutional Review Board of the University of California Los Angeles (UCLA IRB#18-001789) in 2018 and the National Ethics Committee for Health Research in Cambodia (NECHR #010) in 2019. All study volunteers provided verbal and written consents and understood that no identifying information or blood sample had been collected or stored.

3.4. Results

We had a total of 2882 study participants, aged between 30-78 years. We presented in **Table 3-1** the study population's characteristics of PLWH and the general population, among those who had FRS < 10% (i.e. low 10-year CVD risk) and those with FRS ≥ 10% (i.e. moderate to high 10-year CVD risk).

We observed that men made up 78% (n=71) and 62% (n=379) of our study sample, among PLWH and the general population, respectively, among those with moderate-to-high 10-year CVD risk. In the low 10-year CVD risk, however, female participants accounted for about 77% in both population groups. The mean age for both groups was 43 years for those in the low 10-year CVD risk category, but was older for those in the moderate-to-high 10-year CVD risk category, although much older for the general population (57 years, SD=8) than PLWH (54 years, SD=8). Regardless of their 10-year CVD risk, lower educational background was more common among the general population, while unemployment was more prevalent among PLWH. We also noted that the majority of participants from both groups reported living in the provinces, but this was more significant among the general population in both low and moderate-to-high 10-year CVD risk groups.

In addition, we showed the distribution of CVD risk – low, moderate and high – among the study population by age groups in **Figure 3-1**. For both groups, the youngest age group (30-44 years) saw extremely low percentage of participants classified as having moderate (FRS between 10% and 20%) and high (FRS > 20%) CVD risk in the next 10 years; the majority of them were at low 10-year CVD risk (FRS < 10%) **(Figure 3-1)**. However, the percentage went up as the age increased. Slightly more general population than PLWH in the 45-54 age group were in moderate and high 10-year CVD risk. However, in the 55+ group, more PLWH had moderate (34% (n=22)) and high (27% (n=17)) 10-year CVD risk, compared with 31% (n=218) for moderate and 24% (n=168) for high 10-year CVD risk among the general population.

CVD behavioral and metabolic risk factors

Among those who had moderate-to-high 10-year CVD risk, heavy alcohol consumption was more frequent among the general population, 24% (n=56), compared with 11% (n=6) in PLWH, while low physical activity was more frequent among PLWH, 27% (n=14), vs. 16% (n=55) in the general population. Smoking prevalence was similar, 44% (n=40) in PLWH, vs. 40% (n=249) among the general population).

In terms of metabolic risk factors, we observed that, with the exception of diabetes (and prediabetes), compared with PLWH, more general population participants were overweight/obese, 48% (n=294), vs. 28% (n=26) among PLWH. Details of both behavioral and metabolic risk factors for CVD can be found in **Table 3-1**.

We also presented the distribution of CVD metabolic risk factors only among those who were estimated to have moderate-to-high 10-year CVD risk in **Figure 3-2**. We noted a significantly larger proportion of PLWH (than the general population) with prediabetic condition had been estimated to have moderate-to-high 10-year CVD risk.

Distribution of HIV-specific factors by estimated 10-year CVD risk

In **Table 3-2**, we noted that, regardless of their 10-year CVD risk category, our PLWH were mostly on (Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) regimen, while regimen with Protease Inhibitors (PIs) accounted for 5% or less. Other HIV-specific factors were mostly characteristics compatible with prevalent HIV cases (larger proportion of those living with HIV ≥ 60 months and having been on ART ≥ 24 months). However, there appeared to be no association between any HIV-specific factors and moderate-to-high 10-year CVD risk **(Table 3-2)**.

Association between 10-year CVD risk and HIV status

We reported in **Table 3-3** the crude and adjusted odds ratios (ORs) examining the relationship between moderate-to-high 10-year CVD risk among the general population and those living with HIV from two separate models with slightly different sets of adjustment variables. One included in adjustment sex, age, residence location, behavioral and metabolic disorders (high blood pressure, high blood glucose and total cholesterol levels), while the other excluded these metabolic disorders. In both models, the odds of having a 10-year CVD-FRS ≥ 10% were comparable between PLWH and the general population, aOR=0.68 (95% CI: 0.44, 1.05), for the model included metabolic disorders, and aOR=0.88 (95% CI: 0.60, 1.29), for the model excluded them.

3.5. Discussion

Although increased CVD risk had been linked with HIV infection and ART in several large cohort studies, this association was not consistent across all studies (95). Our overall findings suggested that PLWH did not appear to be at higher odds of CVD events in the next 10 years than the general population.

Although we did not show the results, the average FRS was 5.66% among PLWH and 7.64% among the general population. A 2013 study in South Korea reported similar results with the average 10-year CVD risk of 7.07% and 6.87% among PLWH and participants who were HIV-negative, respectively (91). Several past studies with similar findings suggested that many PLWH were considered a low risk group (i.e. they generally had lower prevalence of CVD traditional risk factors, such as smoking and overweight/obesity) and that this could possibly explain a low predicted 10-year risk among this population compared with the general population (91). The fact that PLWH were actually in regular care (in the context of their HIV infection) might have a good influence on their lifestyle behaviors. The majority of PLWH (96% (n=481) reported having received three or more lifestyle advices form their providers in the last 3 years, while only 41% (n=970) of the general population reported so (result not shown).

PLWH in our study sample consisted mainly of those who had been living with HIV for at least 60 months; the average duration of HIV infection was about 10 years **(Table 3-2)**. There was little contrast in terms of ART regimen, making it impossible to examine if the predicted risk differs significantly across the ART drug regimens. However, a few past studies found no significant difference in the predicted CVD risk and ART regimen (91, 96).

On the contrary, another South Korean study published in 2017 (Kim et al.) found that, according to their calculated FRS, a larger percentage of PLWH had higher moderate-to-high 10 year CVD risk (i.e. FRS of 10% or higher) compared with the general population (29.3% vs. 19.5%), even though they eventually concluded that the difference was not statistically "significant" (85). It should be noted that the distribution of traditional risk factors presented in this study by Kim et al. was quite different in their study population compared to ours. About 70% of their study population were smokers (regardless of HIV status), and mean BMI as well as mean fasting blood glucose were higher among PLWH compared with those who were HIV-negative (91). The general population in our study, however, had similar mean BMI to that of PLWH (approximately 22), but lower fasting blood glucose, and slightly higher smoking prevalence (17% vs. 15% in PLWH). A substantially different prevalence of smokers in our study and a study by Kim et al. described earlier (91) could explain a larger proportion of PLWH with of high 10-year CVD risk among their PLWH compared to ours.

We would like to also emphasize that our general population group came from a household STEP survey, it might have been the case that the survey selectively captured a lot more population who were not healthy and, therefore, more likely to be home.

Limitations

There are also several limitations to our study. First, the equations we used to calculate CVD risk score in the present study did not take into account HIV-specific factors, such as CD4 cell count or ART regimen, and had not been validated for use in PLWH. Nevertheless, the risk prediction model that incorporated HIV-specific factors (D:A:D model) had not been validated for PLWH and some also argued that the model's predictive ability did not appear to improve even after adding these HIV-specific factors (43). Second, despite the lack of validation of the D:A:D risk prediction model for use in PLWH population, the use of FRS to predict the 10-year CVD risk among PLWH had not been a general consensus. Recalibration of the FRS might still be necessary for a better risk predictive ability. However, as of 2017, the European Clinical Aids Society's (ECAS) guideline still recommended the use of FRS for PLWH for their CVD risk assessment (97). Furthermore, the FRS had been validated in Chinese population and widely tested in European and North American populations (38). Lastly, because we were not able to ascertain the HIV status for our participants in the general population, misclassification of HIV status might have occurred to some degrees. Nevertheless, the prevalence of HIV among the general population is less than 1% in Cambodia, the amount of misclassification, if there is any, seems to be too small to alter any associations we observed.

Conclusion

Based on the Framingham CVD risk prediction models, PLWH appeared to be as likely as the general population to have moderate-to-high CVD risk in the next 10 years. However, a lot more prediabetic PLWH than the general population were estimated to have moderate-to-high 10-year CVD risk. This underlines the possible complex interaction between different behavioral/metabolic risk factor, biologic factors and HIV-specific factors. PLWH might be at high risk of CVD events in the future with elevated blood glucose levels even when they are not yet diabetic. Therefore, provided that PWLH undergo regular medical check-up as part of their HIV care, regularly perform CVD risk stratification while focusing on modifiable lifestyle behaviors and/or simple medical interventions (if applicable) could help combat present and future morbidity and mortality related to NCDs as well as CVD among this population.

3.6. Tables and figures

Table 3-1. Key characteristics of study participants by their estimated 10-year CVD risk, STEPS, Cambodia, 2015/2016.

	FRS < 10%				FRS ≥ 10%			
	PLWH (n=408)		General Population (n=1768)		PLWH (n=91)		General Population (n=615)	
Characteristics								
Socio-demographics	n	%	n	%	n	%	n	%
Gender								
Male	95	23.3	411	23.3	71	78.0	379	61.7
Female	313	76.7	1357	76.8	20	22.0	235	38.3
Age (mean, SD)	(43.3, 6.8)		(43.7, 10.0)		(53.6, 7.6)		(57.0, 7.7)	
30-44	236	57.8	1004	56.8	8	8.8	37	6.0
45-55	147	36.0	451	25.5	44	48.4	192	31.2
55+	24	5.9	313	17.7	39	42.9	386	62.9
Education								
None or less than primary	96	23.5	1154	65.3	15	16.5	409	66.5
Completed primary	200	49.0	352	19.9	45	49.5	117	19.1
Completed secondary	96	23.5	182	10.3	23	25.3	65	10.6
Completed high school or higher	16	3.9	79	4.5	8	8.8	24	3.9
Occupation								
Salary employed	120	29.4	162	9.2	30	33.0	49	8.0
Self-employed	186	45.6	1348	76.2	40	44.0	469	76.4
Unemployed	102	25.0	258	14.6	21	23.1	97	15.8
Marital status								
Single	3	0.7	63	3.6	1	1.1	10	1.6
Married+cohabiting	246	60.3	1399	79.1	65	72.2	485	78.8
Separated	5	1.2	48	2.7	1	1.1	5	0.8
Divorced	32	7.8	46	2.6	5	5.6	11	1.8
Widowed	122	29.9	212	12.0	18	20.0	104	16.9
Residence location								
Province	302	74.0	1680	95.0	69	75.8	575	93.5
Phnom Penh	106	26.0	88	5.0	22	24.2	40	6.5
CVD behavioral risk factors								
Smokers	34	8.3	154	8.7	40	44.0	249	40.5
Heavy drinkers	11	7.1	130	21.7	6	11.3	56	23.8
< 5 servings of fruits and vegetables	367	90.2	924	52.7	88	96.7	341	55.9
Low physical activity	82	32.2	142	17.4	14	26.9	55	16.0
CVD metabolic risk factors								
Body Mass Index (BMI)								
Normal weight	238	58.5	772	44.7	53	58.2	261	42.4
Underweight	85	20.9	243	14.1	12	13.2	60	9.8
Overweight and obese	84	20.6	712	41.2	26	27.5	294	47.8
Blood glucose								
Prediabetes	203	52.7	271	16.6	47	69.1	86	19.9
Diabetes	21	5.2	48	2.9	23	25.3	135	23.8

Table 3-1. Key characteristics of study participants by their estimated 10-year CVD risk, STEPS, Cambodia, 2015/2016. (continued)

Characteristics	FRS < 10%				FRS ≥ 10%			
	PLWH (n=408)		General Population (n=1768)		PLWH (n=91)		General Population (n=615)	
	n	%	n	%	n	%	n	%
Blood pressure								
Prehypertension	109	29.4	569	37.7	35	57.4	157	56.3
Hypertension	36	8.9	246	14.0	30	33.0	336	54.6
Total cholesterol								
Borderline-high	64	16.3	449	33.1	27	30.7	149	34.8
High	13	3.2	323	19.2	3	3.3	162	27.4

SD, Standard Deviation.

Table 3-2. HIV-specific factor distribution among PLWH, by estimated CVD risk status (based on FRS calculation), STEPS, Cambodia, 2015/2016.

HIV-specific factors	Estimated 10-year CVD risk	
	Low (n=408)	Moderate-to-high (n=91)
	n (%)	n (%)
On ART 24 months or longer	379 (95.5)	83 (95.4)
> 350 CD4 cell count	238 (67.2)	54 (65.9)
ART regimen		
NRTI and NNRTI	372 (97.4)	81 (95.3)
With PI	10 (2.6)	4 (4.7)
Living with HIV ≥ 60 months	356 (87.3)	78 (85.7)
Duration of HIV infection (mean, SD)	9.8 (5.5)	9.7 (4.9)

NRTI, Nucleoside Reverse Transcriptase Inhibitor.
NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor.
PI, Protease Inhibitor.

Table 3-3. Association between moderate-to-high 10-year CVD risk and HIV, STEPS, Cambodia, 2015/016.

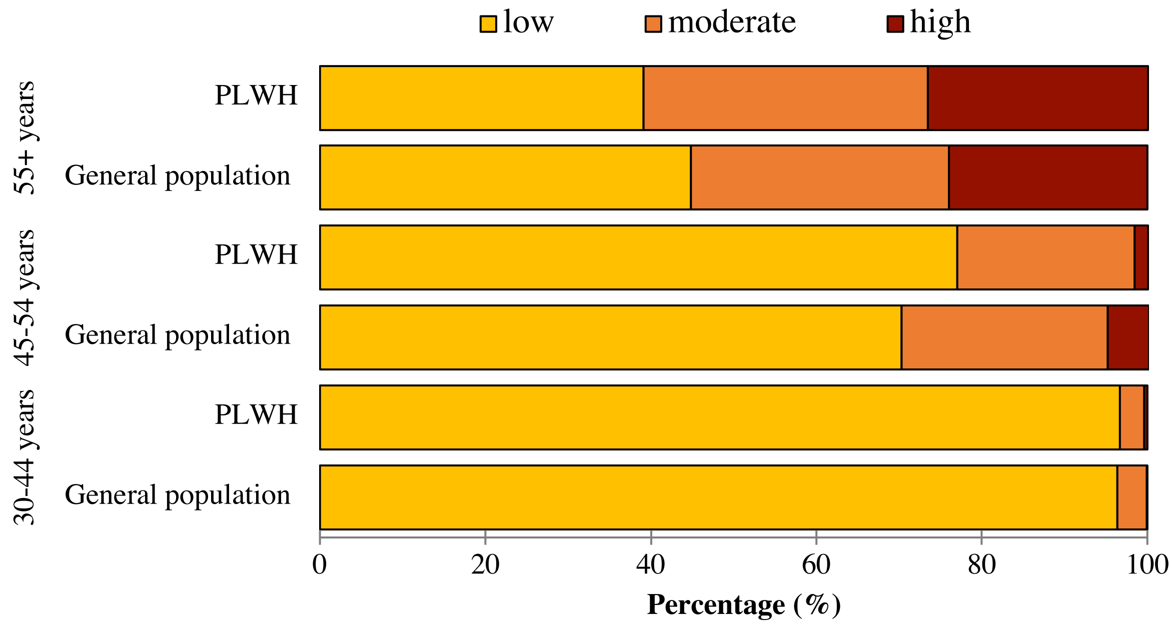
Predictors	Crude OR (95 % CI)	Adjusted OR† (95 % CI)	Adjusted OR‡ (95 % CI)
HIV+ (ref. general population)	0.64 (0.50, 0.82)	0.68 (0.44, 1.05)	0.88 (0.60, 1.29)
Female (ref. male)	0.17 (0.14, 0.21)	0.03 (0.02, 0.04)	0.05 (0.03, 0.06)
Age	1.15 (1.14, 1.17)	1.28 (1.25, 1.31)	1.25 (1.23, 1.28)
Currently living in Phnom Penh (ref. provinces)	0.98 (0.73, 1.33)	0.79 (0.47, 1.30)	0.97 (0.62, 1.52)
2 or more behavioral risk factors¶	2.92 (2.40, 3.55)	3.43 (2.45, 4.81)	3.01 (2.21, 4.09)
BMI (ref. normal weight)			
Underweight	0.71 (0.53, 0.94)	0.39 (0.25, 0.62)	0.29 (0.20, 0.44)
Overweight and obese	1.29 (1.08, 1.55)	1.81 (1.33, 2.46)	2.38 (1.81, 3.15)
Blood pressure (ref. normal)			
Hypertension or prehypertension	4.73 (3.87, 5.77)	6.48 (4.67, 8.99)	-
Blood glucose (ref. normal)			
Diabetes or prediabetes	2.13 (1.78, 2.55)	2.45 (1.80, 3.33)	-
Total cholesterol (ref. normal)			
High or borderline-high	1.44 (1.21, 1.71)	0.98 (0.73, 1.31)	-

CI, Confidence interval.

† Adjusted for sex, age, residence location, behavioral risk factors, BMI, diabetes/prediabetic conditions and high/borderline-high cholesterolemia.

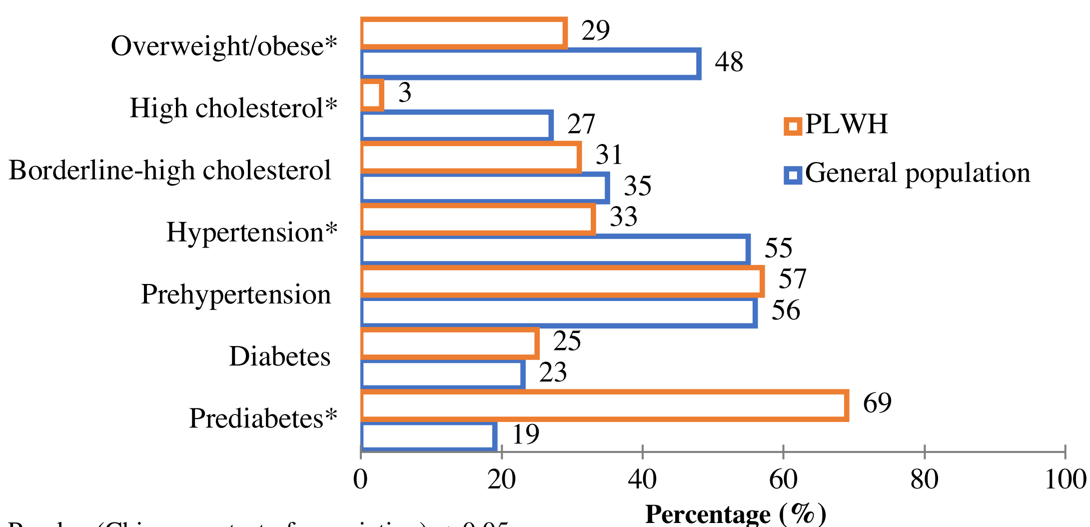
‡ Adjusted for sex, age, residence location, behavioral risk factors and BMI.

¶ Behavioral risk factors include smoking, heavy alcohol consumption, less than 5 servings of fruits and vegetable consumption and low physical activity.



Source: Data from the 2016 UHS (n=2383) and 2015 KHANA (n=499) STEP surveys, Cambodia

Figure 3-1. Distribution of 10-year CVD risk among study participants by age.



* P-value (Chi-square test of association) ≤ 0.05

Source: Data from the 2016 UHS (n=2383) and 2015 KHANA (n=499) STEP surveys, Cambodia

Figure 3-2. Distribution of metabolic risk factors among those with moderate-to-high 10-year CVD risk.

Chapter 4. Study 3: Differences in prevalence and risk factors of non-communicable diseases between young people living with HIV (YLWH) and young general population in Cambodia

4.1. Abstract

Background: Young people living with Human Immunodeficiency Virus or HIV (YLWH) in Cambodia are a vulnerable, understudied population. The demographic transition, HIV infection and its treatments put YLWH more at risk of non-communicable diseases (NCDs). We examined the prevalence of NCDs and their risk factors among YLWH and the young general population to understand the extent to which HIV contributes to the development of NCDs among YLWH.

Design: Cross-sectional survey.

Methods: We gathered information on YLWH, aged 18-29 years, from three HIV clinics in Phnom Penh (n=370), and on young general population from the 2016 survey (n=486) conducted by the University of Health Science. Both surveys employed a standardized questionnaire and physical/biochemical measurement protocols developed by the World Health Organization (STEPwise Approach to Surveillance or STEP survey or STEPS). We reported the prevalence of hypertension, prehypertension, diabetes, prediabetes, high and borderline-high cholesterolemia among the two groups, then performed logistic regression to examine the relationship between each of these conditions and HIV, adjusting for age, sex, residence location, behavioral risk factors and body mass index (BMI).

Results: The prevalence of diabetes and hypertension is 4% (n=16) and 6% (n=22), respectively, among YLWH, compared to 1% (n=4) and 4% (n=22), among the general population of the same age group. YLWH, however, had high prevalence of high cholesterolemia, 20% (n=72), compared with young general population 11% (n=49). In logistic regression, after adjustment, we observed higher odds of diabetes/prediabetes and high cholesterolemia among YLWH

compared with the general population, aOR=6.64 (95% CI: 3.62, 12.19) and aOR=7.95 (95% CI: 3.98, 15.87), respectively.

Conclusion: Results from current study highlight the necessary establishment of screening measures and readily-available treatment options for certain chronic conditions such as diabetes (and prediabetes) and high cholesterolemia, in order to combat high burden of NCDs in the near future among this population.

4.2. Introduction

Adolescents and young adults face major under-addressed behaviors that might pose detrimental effects for their adult health status and prevent them from reaching their full potentials (98). Many of these unhealthy behaviors, such as smoking, substance abuse, exercising and eating habits, were adopted or formed during adolescence and early adulthood, potentially predisposing this population to an early obesity (and their related co-morbidities) and eventual poor health outcomes in their late adulthood (46-49, 98, 99). In addition, unhealthy lifestyle behaviors related to non-communicable diseases (NCDs) have been observed to be more common among youth around the world, prompting even the World Health Assembly to call upon its member states to address NCD-related issues among young people (99).

We focus on adolescents for multiple reasons. First, according to the developmental origins of health and disease theory, the period during adolescence and young adulthood is considered one of the critical periods of for targeting behavioral or medical intervention, as these early interventions could maximize the health benefits that would come later in adulthood, i.e. preventing the development of chronic diseases (100). Second, these NCDs are fast becoming a pressing matter for young people as many of the behaviors that had been associated with NCDs and their risk factors are quite prevalent among young people. According to the World Health

Organization (WHO), "over 150 million young people smoke, 81% adolescents don't get enough physical activity, and 11.7% of adolescents partake in heavy episodic drinking" (49). Lastly, by addressing NCDs among young population now, we are helping to steer the future course of NCD morbidity and mortality. This will have economic and logistical consequences on the healthcare system, which is particularly fragile in resource-limited settings.

In Cambodia, studies conducted in the past have often emphasized specific high-risk populations, rather than the youth population as a whole, and this especially in the context of Human Immunodeficiency Virus (HIV), rather than NCDs (52-59). Moreover, there is increasing evidence implicating HIV infection and antiretroviral therapy (ART) in contributing to the increased risk of multiple chronic metabolic disorders. These include the glucose (87), and lipid disorders for people living with HIV, particularly those in older age (101, 102).

Because of inadequate research among YLWH in Cambodia, the risk profile and prevalence of NCDs among our YLWH had never been comprehensively assessed. The lack of epidemiological research among this vulnerable population should not be overlooked.

Therefore, the present study aimed to examine the differences (or similarities) among YLWH and the general population of the same age group in terms of their distribution of NCDs, as well as NCD risk factors, to inform research and health policy priorities, as well as to determine if specific and early behavioral or medical interventions should be prepared for this young population.

4.3. Methods

Study setting and recruitment

We conducted a cross-sectional survey and recruited 370 YLW who came for regular medical checkup at three HIV clinics in Phnom Penh, Cambodia, from November 2019 –

February 2020. In Cambodia, these clinics/hospitals are known as Opportunistic Infections and Antiretroviral Therapy sites, designated “OI/ART” sites.

Information on the general population, on the other hand, was obtained from a subset of the STEP[7] (household) survey population of the same age group (n=486), which was conducted across all provinces in Cambodia by the University of Health Sciences (UHS) and partners in 2016.

Both our newly-conducted STEP survey and the 2016 STEP survey gathered information on socio-demographics and NCD risk factors, such as smoking, alcohol consumption, diet and physical activity. Our STEP survey, however, added information on HIV-specific factors, such as ART regimen and duration of ART use, using (de-identified) patients’ personal follow-up booklet and/self-reports.

Participants of both sexes were considered eligible if they were between the age of 18-29 years and were able to provide verbal consent to the study team at the time of data collection.

All data collectors underwent training prior to data collection regarding interviewing techniques and ethical research principles with human subjects certified trainers. They were also trained on study protocol, tablet usage, and measurement techniques/protocols to ensure consistency in data collection process.

Data collection tools and process

We conducted a Computer-Assisted-Person-Interview (CAPI) using tablets for the 370 YLWH recruited for our study.

[7] The World Health Organization (WHO) developed a standardized questionnaire and measurement protocols for the surveillance of NCDs and their risk factors, called STEP survey or STEPS.

To obtain physical and biochemical measurements on our study volunteers, we employed digital scales, OMRON® Upper Arm Blood Pressure Monitor, measuring tapes and BeneCheck® rapid testing devices. Of note, blood pressure was measured three times, five minutes apart, and the average of the three was then calculated. The rapid blood tests (for glucose and total cholesterol levels) took less than a minute. Information on whether or not participants fasted the night before was also noted for later glucose adjustment for diabetes and prediabetes classification.

Physical activity (recreation- or work-related) included locally-adapted activities, such as farming and household chores. Body Mass Index (BMI) classification was based on Asian-specific cutoffs.

In general, when the participant had been (verbally) consented, they would be measured (weight, height, waist circumference, and blood pressure). Then they underwent rapid blood tests (whether or not the participant had been fasting before blood tests will also be noted) so that values will be adjusted later for diabetes and prediabetes classification. After physical and biochemical measurements, results of these measurements were given back to each participant in written letter in case they would like to further discuss with their healthcare provider. In the end, the data collector would conduct a face-to-face interview with each individual using a structured questionnaire which was administered via tablet.

Definition and classification (72-76)

Definition and classification of variables are as follow: **1)** smokers refer to current (daily or not) users of any tobacco products. **2)** heavy drinkers refer to those who had, during the past week: 4 standard drinks[8] or more on any one occasion or 14 standard drinks or more in total (men), or 3 standard drinks or more on any one occasion or 7 standard drinks or more in total (women). **3)** fruit and vegetable consumption refer to any one-day consumption on a typical week within the past year. **4)** low physical activity refers to less than 75 minutes of work or recreation activity of vigorous intensity per week or less than 150 minutes of recreation activity of moderate intensity per week. **5)** nutritional status – underweight refers to BMI < 18.5, normal weight refers to BMI between 18.5 and 23, overweight and obese refers to BMI ≥ 23 and BMI ≥ 25, respectively. **6)** Hypertension: mean systolic blood pressure (SBP) ≥ 140 mmHg and/or mean diastolic blood pressure (DBP) ≥ 90 mmHg and/or on anti-hypertensive drugs. **7)** Diabetes: fasting glucose ≥ 126 mg/dL or post-prandial glucose ≥ 200mg/dL and/or on anti-diabetic drugs. **8)** Prediabetes: fasting glucose between 101-125 mg/d or post-prandial glucose between 140-199 mg/dL. **9)** Prehypertension: mean SBP between 120-139 mmHg and/or mean DBP between 80-89 mmHg. **10)** High cholesterolemia: total cholesterol between ≥ 240 mg/dL and/or on cholesterol lowering drugs. **11)** Borderline-high cholesterolemia: total cholesterol between 200-239 mg/dL.

Power calculation and statistical analysis

With the total sample size of 856 (370 of YLWH and 486 of the general population), the present study has more than 90% power to detect a difference in prevalence of diabetes, prediabetes, high and borderline-high cholesterolemia, between the two groups.

For analysis, we calculated the prevalence of hypertension, prehypertension, diabetes, prediabetes, high and borderline-high cholesterolemia as well as percentages and means for

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[8] A standard drink is defined as one with a net content of approximately 10g of pure ethanol (in accordance with the WHO's STEP survey showcards' contents).

categorical and continuous variables, respectively, among YLWH and the general population. We fitted a separate logistic regression model to examine the association between each of the conditions listed above and HIV; we reported the crude and adjusted odds ratios (ORs), the latter controlled for other covariates including age, sex, residence location (Phnom Penh vs. provinces), behavioral risk factors (smoking, heavy drinking, less than 5 servings of fruits and vegetables, low physical activity) and BMI. All analyses were performed using STATA 14 (Copyright 1985-2015 StataCorp LLC).

Ethical considerations

The current study was approved by the Institutional Review Board of the University of California Los Angeles (UCLA IRB#19-000272) and the National Ethics Committee for Health Research in Cambodia (NECHR #129) in 2019. All study volunteers provided verbal and understood that no identifying information or blood sample had been collected or stored.

4.4. Results

Socio-demographics

Overall, there were 370 participants who were living with HIV and 486 general population participants (total N=856) aged between 18-29 year. **Table 4-1** detailed all the socio-demographics and the NCD risk factor distribution.

We found that about 70% (n=254) of participants who are living with HIV were male, whereas, female participants accounted for 70% (n=344) of the general population. The average age was 23 years (SD=3.2) and the median was 23 years (IQR=6) among YLWH, while the average and median age were 24 years (SD=3.3) and 25 years (IQR=6), respectively, among the general population. In terms of education, more YLWH reported having had completed at least high school (58% (n=210)) while only 15% (n=72) of the young general population reported so.

However, those who were unemployed accounted for about 20% in each group, the rest was either self- or salary-employed. We also noted a huge difference in terms of residence types reported between the two groups. About 95% (n=468) the young general population, but only 23% (n=85) of YLWH reported that their current residence was in the provinces.

NCD risk factor distribution

We observed that the prevalence of smoking was low (less than 10% in both groups) and heavy alcohol consumption differed only slightly among the two groups (20% (n=52) among YLWH vs. 23% (n=37) among the general population). Although consumption of low fruits and vegetable consumption and low physical activity were more common among YLWH compared to the young general population, we observed that the number of those who were overweight and obese were higher in the young general population group (24% (n=109)) than YLWH (16% (n=57)) **(Table 4-1)**. Obesity was 7% (n=24) among YLWH and 12% (n=55) among the general population (result not shown). The prevalence of diabetes and hypertension is 4% (n=16) and 6% (n=22), respectively, among YLWH, compared to 1% (n=4) and 4% (n=22), among the general population. In addition, YLWH presented more prevalent cases of high total blood cholesterol (20% (n=72)) compared with the young general population (11% (n=49)). Other metabolic abnormalities are elaborated in **Table 4-1**.

We presented in **Table 4-2** the distribution of HIV-specific factors by glucose, blood pressure and total cholesterol status. Of note, only high or borderline-high cholesterolemia emerged to be associated with longer duration of ART use (24 months or longer), combination NRTI and NNRTI therapy, perinatal HIV infection and longer duration of HIV infection (60 months or longer) **(Table 4-2)**. For further illustration, we also presented in **Figure 4-4** the distribution of these HIV-specific factors among those with normal and elevated total cholesterol levels.

Association between NCDs and HIV

Diabetes or prediabetes

We grouped diabetes or prediabetes in order to ensure sufficient number of outcomes across exposure status and other adjusting variables (the number of diabetic cases alone is low in both groups). Without adjusting for potential confounders, YLWH were nine times more likely than the general population to present diabetes or prediabetes, cOR=9.59 (95% CI: 6.15, 14.95). After adjusting for potential confounders (sex, age, current residence location, behavioral risk factors and BMI), YLWH remained at significantly higher odds of diabetes or prediabetes compared with the general population, aOR=6.64 (95% CI: 3.62, 12.19) (**Table 4-3**).

We also presented the boxplots depicting the relationship between fasting plasma glucose levels and HIV, stratifying on BMI status and sex in **Figure 4-1** and **Figure 4-2**, respectively. Regardless of BMI and sex, YLWH appeared to have a higher fasting plasma glucose levels compared to the young general population.

Hypertension and prehypertension and HIV

In crude analysis, the crude ORs appeared to suggest a positive association between both hypertension and prehypertension and HIV, cOR=1.60 (95% CI: 1.17, 2.18) and cOR=1.36 (95% CI: 0.74, 2.50), respectively. However, after adjustment was made **(Table 4-4)**, YLWH were no longer at higher odds of these conditions compared with the young general population, aOR=1.01 (95% CI: 0.59, 1.71) for prehypertension and aOR=0.41 (95% CI: 0.13, 1.27) for hypertension.

High and borderline-high cholesterol

We presented in **Table 4-5** the association between total cholesterol levels and HIV among ALL study participants (including those who did not fast before rapid blood tests). YLWH were twice (before adjusting for covariates) and almost eight times (after adjustment) more likely than the young general population to present high cholesterolemia, the crude and adjusted ORs were, respectively, cOR=2.04 (95% CI: 1.37, 3.02) and aOR=7.95 (95% CI: 3.98, 15.87). The odds of borderline-high cholesterolemia did not appear to be different among the two groups, aOR=0.98 (95% CI: 0.45, 2.15). Although we showed here only the results among ALL participants for high and borderline-high cholesterolemia, all of these above associations between total cholesterol and HIV remained largely unaffected with or without inclusion of those who did not fast before rapid blood tests.

We also showed in **Figure 4-3** the (fasting) total cholesterol levels among study participants by BMI status and sex. Higher total cholesterol was observed among YLWH regardless of sex and BMI status.

4.5. Discussion

Our findings on NCDs confirm that from other studies conducted in different parts of the world, although few have examined young people living with HIV under the same age range as ours (18-29 years).

First, the prevalence of hypertension was 6% among our YLWH, which is lower than the 8% and 12.4% reported in Ugandan studies conducted in Rakai and Lubowa, respectively (103, 104). However, these two studies recruited a much older population, the mean age for the Rakai study population was about 38 year for women and 42 years for men (103), both of which are more than 10 years older than our YLWH's mean age. The population under study in Lubowa, on the other hand, was composed of only 11% of those under the age of 30 (104). Because age is known to be positively associated with high blood pressure regardless of HIV status, we would expect a lower prevalence in our study compared to theirs.

We also found comparable diabetes prevalence in our study (4.6%) as the study conducted in Lubowa (Uganda) which reported a prevalence of 4.7% (104). However, taking into account the difference in the age constitution of both study populations (much older PLWH in their study compared to ours), it is likely that the actual prevalence between the two studies might have been different. Additionally, the study in Lubowa defined diabetes with a much higher threshold of fasting plasma glucose (140 mg/dL or higher), leading to a small number of diabetes cases (104), despite having a much older population in the study.

However, a recently published paper, using data collected from HIV clinics at the University of Maryland Medical System and the University of Maryland Family Medicine Program, reported a much higher prevalence of hypertension (23.1%) but a lower prevalence of diabetes (2% to 4%) compared to ours (105). Although this study was also conducted among those aged between 18-29 years, the smoking and alcohol consumption rates were very high (about 60% for both) (105).

We noted higher prevalence of high cholesterolemia in our YLWH, contrasting to findings from the 2015 STEPS, conducted among older PLWH (14). This could be due to an increase in the Protease-Inhibitor- or PI-based regimen use among children (from only 5% in 2009[9] to 13%in 2016[10], based on reports from the National Center for HIV/AIDS, Dermatology and STDs (NCHADS). PIs were frequently linked with dyslipidemia (37, 45).

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[9] Annual Report 2009. MOH/NCHADS. Cambodia. 2009.
[10] Annual Report 2016. MOH/NCHADS. Cambodia. 2016.

Second, our general population group came from a household STEP survey, it might have been the case that the survey selectively captured a lot more population who were not healthy and, therefore, more likely to be home.

Third, the difference in traditional (behavioral) risk factor distribution among population living with HIV could be due partially to difference in income levels and other demographic factors in different study settings might as well explain these differences in NCD prevalence across studies. About 70% of our YLWH were men, a finding that is also contrasting to that of the 2015 STEP survey conducted among older PLWH in Cambodia (14). However, our survey was conducted only in Phnom Penh (capital city) and our study population was also much younger. As the country increasingly opens up to gay and transgender community and more HIV clinics begin to offer services tailored to their health needs, more of these individuals also start coming out and seeking care. Therefore, the 2015 STEP survey captured an older generation of PLWH (a lot of whom had been infected behaviorally), while our study population was a younger generation of PLWH (an equal mixture of both behaviorally and perinatally infected individuals).

Lastly, definitions and terms used for each of these conditions might slightly differ from one study to another, and quietly possibly there were variations between blood tests. Other factors related to HIV infection, such as acquiring HIV perinatally or behaviorally **(Table 4-2)** might be associated with other NCD risk factors, and, therefore, also drive some of these differences in NCD prevalence. Although, there appeared to be no association between any of these HIV-specific factors and elevated blood glucose or blood pressure **(Table 4-2)** and the distribution of NCD behavioral risk factors did not appear to significantly differ among our

YLWH who were perinatally infected and those who were behaviorally infected (result not shown).

Limitations

First, given the nature of our study design, we understand that we have to be careful when interpreting our findings regarding the association between HIV and NCDs, in causal terminology. Nevertheless, these results were consistent with that of multiple studies including those of longitudinal nature, such as the MACS cohort study, affirming the plausibility that the relationship observed here might be close to the underlying true relationship. In addition, about half of YPLW in the study sample were perinatally-infected and the average duration of HIV infection was about 9 years. Taking this as well as their age into consideration, we can reasonably assume that their metabolic disorders are more likely to occur after the onset of HIV infection and ART. Besides, we also saw that the NCD prevalence among those perinatally infected and behaviorally infected did not significantly differ, particularly in the case of diabetes/prediabetes and hypertension/prehypertension.

Second, because we were not able to ascertain the HIV status for our participants in the general population, misclassification might have occurred. However, the prevalence of HIV among the general population is less than 1% in Cambodia, the amount of misclassification (if any) should be negligible.

Third, we lacked detailed lipid profile as our rapid tests were only capable of measuring total cholesterol. Low-density lipoprotein or high-density lipoproteins cholesterol (LDL-Chol or HDL-Chol) as well as triglycerides were not captured. Our study could then only provide first look on the overall fat profile among this population.

Lastly, there were several covariates related to the NCDs that were not measured in the original STEP survey conducted among the general population, including oral contraceptive use (for women) and birth history (prematurity or low birth weight). As a result, we could not account for any of these factors in the analysis. Nevertheless, the focus of the STEP survey is the modifiable lifestyle factors, many of which were indeed included in logistic regression model. Moreover, the majority of our YLWH were males and although we didn't show in results, over 80% of our female participants reported no use of oral contraceptives at the time of data collection.

Conclusion

Young population living with HIV in Cambodia, mainly in the capital city (Phnom Penh), face multiple metabolic disorders and NCDs despite their young age and lower prevalence of traditional risk factors such as smoking and alcohol consumption compared with general population of the same age group. The prevalence of glucose disorders (diabetes and prediabetes) and high cholesterolemia were significantly higher among our YLWH compared with the young general population, while hypertension prevalence between the two groups appeared comparable.

The current study's results highly suggest that HIV infection and ART might have important roles in contributing to the early development of chronic diseases, such as diabetes, prediabetes and high cholesterolemia, in addition to the conventional NCD risk factors. Further investigations including detailed lipid profile assessment (including LDL-Cholesterol, HDL-Cholesterol and triglycerides) might be necessary to fully comprehend the extent to which HIV-specific factors affect various forms of fats. Furthermore, the Cambodian ART regimen guideline needs further exploration and discussions; there needs to be studies that are designed specifically to assess the effects of various ART drugs on these metabolic chronic disorders, especially that of glucose and cholesterol.

Understanding the contributions of these HIV-specific factors to an increase in chronic disease risk and putting in place early proper screening as well as treatment measures for certain metabolic disorders (mainly prediabetes, diabetes and high total cholesterolemia) targeting this young population group might be one of the most effective strategy to combat NCD morbidity and mortality in the long term.

4.6. Tables and figures

Table 4-1. Key characteristics of study participants, STEPS, Cambodia, 2016 and 2019/2020.

Socio-demographics	**YLWH (n=370)**		**Young General Population (n=486)**	
	n	%	n	%
Gender				
Male	254	70.8	146	29.8
Female	105	29.2	344	70.2
Age (mean, SD)	(23.1, 3.2)		(24.1, 3.3)	
Education				
None or less than primary	7	1.9	177	36.1
Completed primary	41	11.4	136	27.8
Completed secondary	101	28.1	105	21.4
Completed high school or higher	210	58.5	72	14.7
Occupation				
Salary employed	211	58.8	64	13.1
Self-employed	70	19.5	312	63.7
Unemployed	78	21.7	114	23.3
Marital status				
Single	315	87.7	149	30.4
Married+cohabiting	40	11.1	322	65.7
Other	4	1.1	19	3.4
Residence types				
Province	85	23.5	468	95.5
Phnom Penh	277	76.5	22	4.5
NCD behavioral risk factors				
Smokers	17	4.7	32	6.5
Heavy drinkers	52	19.6	37	23.3
< 5 servings of fruits and vegetables	232	65.9	245	50.1
Low physical activity	81	38.9	44	20.4

Table 4-1. Key characteristics of study participants, STEPS, Cambodia, 2016 and 2019/2020. (continued)

Characteristics	YLWH (n=370)		Young General Population (n=486)	
NCDs	n	%	n	%
Body Mass Index (BMI)				
Normal weight	210	58.2	251	55.6
Underweight	94	26.0	91	20.2
Overweight and obese	57	15.8	109	24.2
Blood glucose				
Prediabetes†	120	34.0	23	5.2
Diabetes†	16	4.5	4	0.9
Fasting blood glucose‡ (mean, SD)	(105.6, 26.3)		(80.8, 19.6)	
Blood pressure				
Prehypertension	114	31.6	111	23.0
Hypertension	22	6.1	22	4.5
SBP‡ (mean, SD)	(113.4, 12.0)		(110.0, 11.3)	
DBP‡ (mean, SD)	(75.2, 8.1)		(72.4, 9.1)	
Total cholesterol				
Borderline-high†	34	12.2	82	21.0
Borderline-high¶	22	12.9	82	21.0
High†	72	20.4	49	11.2
High¶	47	21.7	49	11.2
Fasting total cholesterol‡ (mean, SD)	(189.4, 63.1)		(179.7, 49.4)	

SD, Standard Deviation.
† Included ALL participants.
‡ Excluded those currently on treatment for each specified condition.
¶ Included ONLY fasting participants.

Table 4-2. Distribution of HIV-specific factors by NCD status, STEPS, Cambodia, 2016 and 2019/2020.

	Diabetes or prediabetes	Hypertension or prehypertension	High or borderline-high cholesterolemia
	n (%)	n (%)	n (%)
On ART 24 months or longer	80 (59.3)	74 (55.2)	79 (75.2)***
Less than 350 CD4 cell count	51 (76.1)	49 (67.1)	30 (69.8)
NRTI and NNRTI (vs. other)	42 (70.0)	49 (65.3)	48 (82.7)**
Perinatally infected (vs. behaviorally infected)	62 (47.0)	58 (43.3)	60 (59.4)**
Living with HIV ≥ 60 months	73 (54.1)	68 (50.7)	71 (67.6)**
Duration of HIV infection (mean, SD)	8.6 (8.3)	8.6 (8.6)	10.9 (8.2)**

NRTI, Nucleoside Reverse Transcriptase Inhibitor.
NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor.
*, **, *** refers to a p-value ≤ 0.05, ≤ 0.01, and ≤ 0.001, respectively.

Table 4-3. Association between diabetes/prediabetes and HIV, STEPS, Cambodia, 2016 and 2019/2020.

	Diabetes or Prediabetes	
Predictors	**Crude OR (95% CI)**	**Adjusted OR† (95% CI)**
HIV+ (ref. young general population)	9.59 (6.15, 14.95)	6.64 (3.62, 12.19)
Female (ref. male)	0.29 (0.20, 0.42)	0.67 (0.44, 1.03)
Age	0.94 (0.90, 1.00)	0.96 (0.91, 1.03)
Current address in Phnom Penh (ref. in provinces)	5.44 (3.76, 7.89)	1.33 (0.81, 2.21)
2 or more behavioral risk factors‡	1.78 (1.17, 2.71)	1.17 (0.73, 1.86)
BMI (ref. normal weight)		
Underweight	0.62 (0.40, 0.99)	0.49 (0.29, 0.81)
Overweight and obese	0.92 (0.59, 1.44)	1.19 (0.72, 1.98)

CI, Confidence interval.

Diabetes: fasting glucose ≥ 126 mg/dL or post-prandial glucose ≥ 200mg/dL and/or on anti-diabetic drugs.

Prediabetes: fasting glucose between 101-125 mg/d or post-prandial glucose between 140-199 mg/dL.

† Adjusted for sex, age, residence location, behavioral risk factors and BMI.

‡ Behavioral risk factors include smoking, heavy alcohol consumption, less than 5 servings of fruit and vegetable consumption and low physical activity.

Table 4-4. Association between hypertension and prehypertension and HIV, STEPS, Cambodia, 2016 and 2019/2020.

	Hypertension		Prehypertension	
Predictors	Crude OR (95% CI)	Adjusted OR† (95% CI)	Crude OR (95% CI)	Adjusted OR† (95% CI)
HIV+ (ref. young general population)	1.36 (0.74, 2.50)	0.41 (0.13, 1.27)	1.60 (1.17, 2.18)	1.01 (0.59, 1.71)
Female (ref. male)	0.36 (0.18, 0.70)	0.38 (0.17, 0.83)	0.31 (0.22, 0.43)	0.28 (0.19, 0.42)
Age	1.12 (1.02, 1.23)	1.09 (0.99, 1.21)	1.06 (1.01, 1.12)	1.06 (1.01, 1.12)
Current address in Phnom Penh (ref. in provinces)	1.91 (1.04, 3.51)	3.54 (1.21, 10.41)	1.41 (1.02, 1.94)	1.18 (0.70, 1.97)
2 or more behavioral risk factors‡	2.12 (1.08, 4.17)	1.70 (0.82, 3.56)	1.19 (0.79, 1.78)	0.89 (0.57, 1.40)
BMI (ref. normal weight)				
Underweight	0.66 (0.21, 2.01)	0.73 (0.24, 2.28)	0.54 (0.35, 0.84)	0.62 (0.39, 0.97)
Overweight and obese	5.27 (2.70, 10.28)	5.18 (2.58, 10.38)	1.94 (1.31, 2.86)	2.15 (1.41, 3.28)

CI, Confidence interval.
Hypertension: mean SBP ≥ 140 mmHg and/or mean DBP ≥ 90 mmHg and/or on anti-hypertensive drugs.
Prehypertension: mean SBP between 120-139 mmHg and/or mean DBP between 80-89 mmHg.
† Adjusted for sex, age, residence location, behavioral risk factors and BMI.
‡ Behavioral risk factors include smoking, heavy alcohol consumption, less than 5 servings of fruit and vegetable consumption and low physical activity.

Table 4-5. Association between high and borderline-high cholesterolemia and HIV, STEPS, Cambodia, 2016 and 2019/2020.

Predictors	High cholesterolemia		Borderline-high cholesterolemia	
	Crude OR (95% CI)	Adjusted OR† (95% CI)	Crude OR (95% CI)	Adjusted OR† (95% CI)
HIV+ (ref. young general population)	2.04 (1.37, 3.02)	7.95 (3.98, 15.87)	0.52 (0.34, 0.81)	0.98 (0.45, 2.15)
Female (ref. male)	2.52 (1.65, 3.83)	5.10 (3.02, 8.60)	3.43 (2.20, 5.35)	3.59 (2.09, 6.14)
Age	1.01 (0.95, 1.07)	1.05 (0.97, 1.12)	1.11 (1.04, 1.19)	1.09 (1.01, 1.16)
Current address in Phnom Penh (ref. in provinces)	1.53 (1.03, 2.26)	0.78 (0.43, 1.42)	0.64 (0.41, 1.01)	1.29 (0.61, 2.71)
2 or more behavioral risk factors‡	1.12 (0.68, 1.86)	1.38 (0.78, 2.45)	0.42 (0.21, 0.84)	0.72 (0.35, 1.49)
BMI (ref. normal weight)				
Underweight	0.88 (0.52, 1.49)	0.69 (0.39, 1.21)	0.36 (0.19, 0.68)	0.32 (0.16, 0.62)
Overweight and obese	1.10 (0.65, 1.87)	1.32 (0.75, 2.33)	1.24 (0.75, 2.20)	1.03 (0.61, 1.72)

CI, Confidence interval.

High cholesterolemia: total cholesterol between ≥ 240 g/dL and/or on cholesterol lowering drugs.

Borderline-high cholesterolemia: total cholesterol between 200-239 g/dL.

† Adjusted for sex, age, residence location, behavioral risk factors and BMI.

‡ Behavioral risk factors include smoking, heavy alcohol consumption, less than 5 servings of fruit and vegetable consumption and low physical activity.

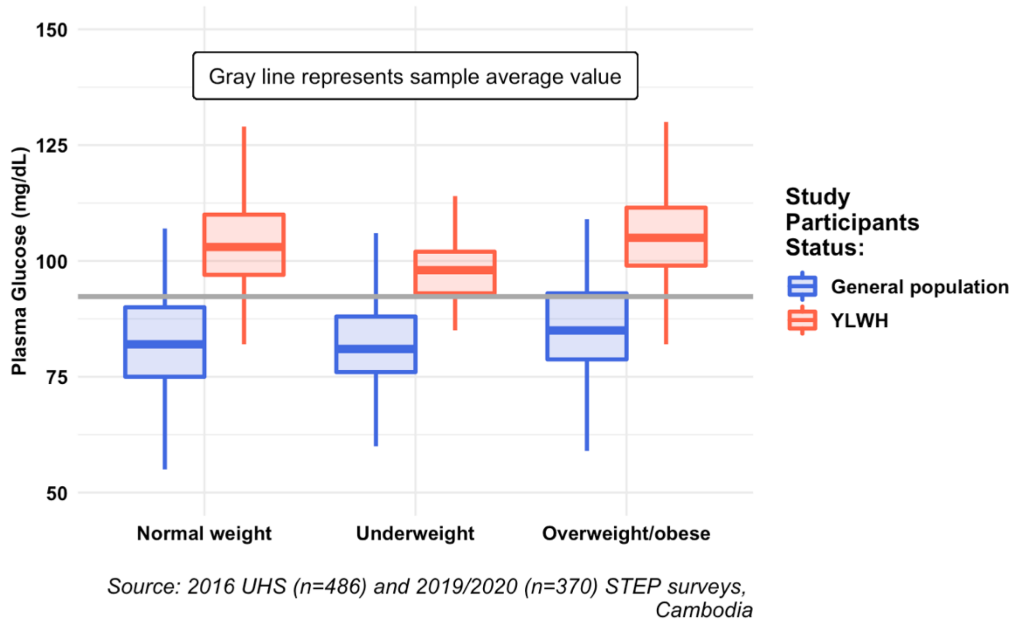


Figure 4-1. Plasma glucose levels among (fasting) study participants, stratified by BMI.

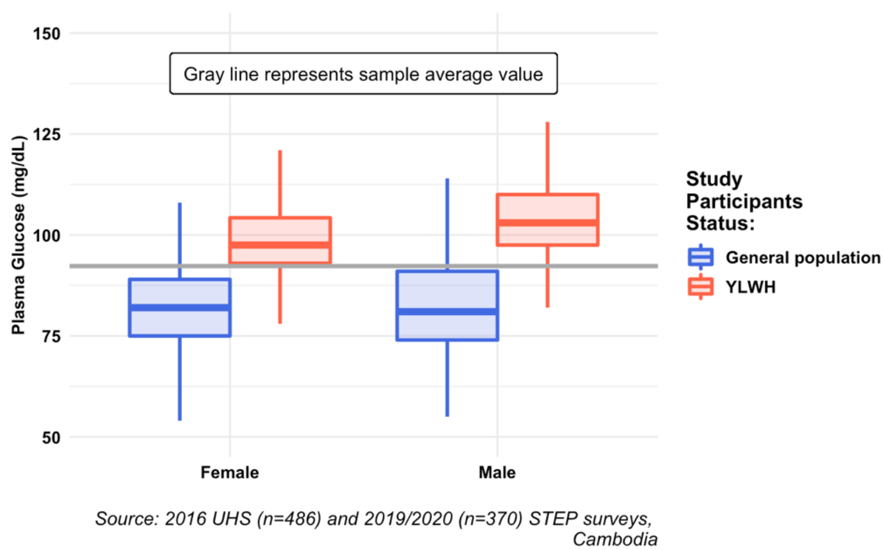
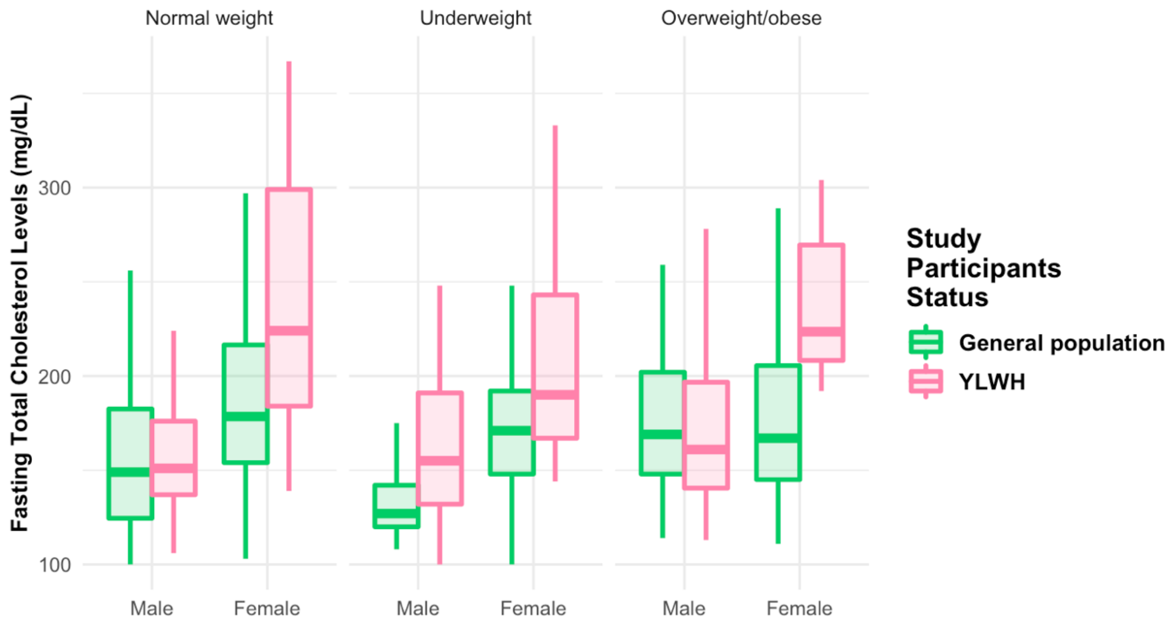
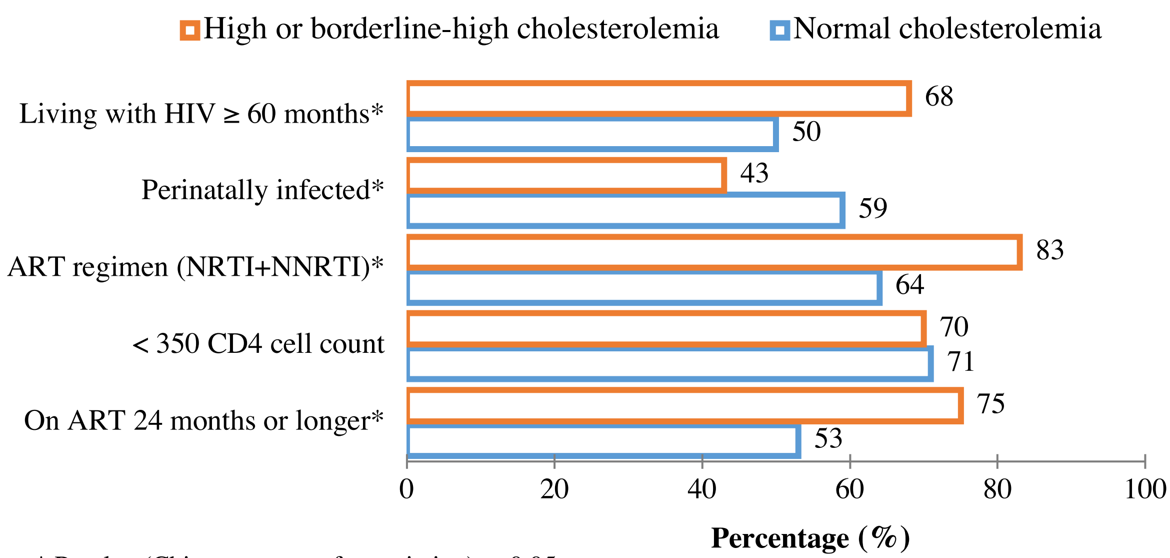


Figure 4-2. Plasma glucose levels among (fasting) study participants, stratified by sex.



Source: 2016 UHS (n=486) and 2019/2020 (n=370) STEP surveys, Cambodia

Figure 4-4. Association between total cholesterol and HIV, stratified by BMI and sex.



* P-value (Chi-square test of association) ≤ 0.05

Source: Data from the 2016 UHS (n=486) and 2019/2020 (n=370) STEP surveys, Cambodia

Figure 4-3. Distribution of cholesterolemia status by HIV-specific factors.

Chapter 5. Public health significance

In Cambodia, research on non-communicable diseases remain limited due to many competing priorities in the health sector, a common scenario among low-middle-income countries (LMICs) which are undergoing demographic and epidemiological transition. Estimating burden of NCDs and assessing their risk factors is an important first step to NCD prevention. For PLWH and the general population alike, this assessment helps inform health research priorities and provides valuable insights into planning research studies and future intervention strategies, such as lifestyle modification and medications.

These three studies contribute as evidence from LMICs, where heavy burden of both communicable and non-communicable conditions often intersect, although the latter is rarely addressed in scientific research publication.

My first and third studies showed that adult PLWH and YLWH were at particularly higher odds of diabetes and prediabetes than the general population and young general population, although the general population group presented higher prevalence of traditional risk factors, such as smoking and heavy drinking. In addition, YLWH (but not the adult PLWH) were at higher odds of high cholesterolemia than the young general population. Although these metabolic disorders are also known to be commonly associated with ART, we found contrasting results among older adult PLWH and YLWH.

Our findings on diabetes and prediabetes justify establishing screening and/or interventional measures among this population as well as further investigations into our current antiretroviral treatment guideline. These measures pertain as well to cholesterolemia as the ART regimen guidelines might be different between older and younger generation of PLWH.

My second study brought attention to cardiovascular disease or CVD among the population in Cambodia. CVD risk assessment is an important tool and the first step to guide prevention efforts and clinical treatments because in resource-limited settings, prevention measures remain the best options. This is particularly true, in the case of CVD, in which the elimination of its major (traditional) risk factors can greatly reduce its risk. Although the odds of moderate-to-high 10-year CVD risk were similar among PLWH and the general population, it is important to regularly perform CVD risk stratification among this population due to the highly prevalent glucose disorders (prediabetes), even in a young age group. Moreover, this population is linked in care, making it easier to start behavioral and/or medical interventions should the risk stratification tool estimate them to be at high risk.

All three of my studies have contributed in terms of scientific knowledge and helped inform health research priorities for both PLWH and YLWH in Cambodia. With more powerful ART drugs, our focus should now be extended beyond viral suppression. Setting up behavioral and medical interventions as well as reinforcing screening efforts for metabolic disorders commonly associated with ART should also be considered as important as viral suppression. There should also be further studies, designed specifically to look into the effects of each ART regimen, both by class and by their individual compounds.

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