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Associations of Chronic Infectious and Non-infectious Disease Comorbidities with HIV Clinical Outcomes

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ABSTRACT

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By

NANG THU THU KYAW

July 22, 2020

Globally, nearly 3% of the 38 million people living with HIV (PLHIV) died in 2018. Underlying comorbidities in PLHIV present critical challenges to clinical care and contribute to increased mortality in PLHIV. Key infectious disease comorbidities include tuberculosis (TB), hepatitis B virus (HBV), and hepatitis C virus (HCV). Given the rapid expansion of type 2 diabetes mellitus (T2DM) worldwide, T2DM is an emerging non-infectious disease comorbidity among PLHIV. All four of these comorbidities are associated with increased mortality in PLHIV. Currently there is an urgent need to develop clinical guidelines for HIV programs that integrate prevention, screening, and treatment for comorbidities. However, existing data that quantifies the impact of comorbidities on HIV outcomes are limited, especially in resources limited settings. To answer critical questions related to the effects of comorbidities on health outcomes in PLHIV, we conducted three observation studies using the clinical data of PLHIV from Myanmar.

In study 1, we assessed biological interaction between hyperglycemia and low body mass index (BMI) on the risk of TB disease among patients entering HIV care. Cox proportional hazard models were used to estimate the rates of TB disease due to hyperglycemia, due to low BMI, and due to joint exposure (hyperglycemia and low BMI). We used continuous, categorical, and spline measures of hyperglycemia and low BMI to model the dose-response relationship with TB incidence. We performed sensitivity analyses to assess the direction and magnitude of bias in estimation of the association between low BMI and hyperglycemia with TB incidence due to unmeasured confounders, exposure misclassification, and competing risks. We reported a biological interaction between BMI and hyperglycemia on the risk of TB disease [relative excess risk of TB disease due to joint exposure: 0.42, 95% CI:0.07, 0.78].

Study 2 focused on the relationship between TB disease and key clinical outcomes in PLHIV, including all-cause mortality, CD4+T cell response, and virological failure. Study 2 also assessed the role of glycemic status as a mediator in the relationship between active TB and all-

cause mortality. This study used log binomial regression, general linear mixed models, and mediation analysis to achieve the analysis objectives. After one-year of follow-up time, we observed an association between active TB with all-cause mortality [adjusted hazard ratio (aHR): 1.75, 95% CI: 1.38, 2.21]. The mean log CD4 cell count during the follow-up was significantly lower in PLHIV with active TB compared to those without active TB [β_{TB} = -0.61, 95% CI: -0.71, -0.51, $\beta_{TB*follow\text{-}up\ month}$= 0.04, 95% CI: 0.03, 0.05]. However, we did not observe glycemic level to be a key mediator in the relationship between TB disease and all-cause mortality.

Study 3 examined whether associations between HBV/HCV coinfection and all-cause mortality differed by hyperglycemia status among PLHIV. We used Cox proportional hazards models to compare all-cause mortality rates in participants by HCV/HBV coinfection and hyperglycemia status. We reported coinfections with hepatitis increased rates of all-cause mortality [aHR: 1.25, 95% CI: 1.11, 1.40] for HBV, 1.52, 95% CI: 1.35, 1.71] for HCV, and 2.14, 95% CI: 1.51, 3.02] for HBV/HCV coinfection compared to HIV mono-infection]. The observed associations were greater in HCV and HBV/HCV coinfected patients with hyperglycemia [aHR: 1.85, 95% CI: 1.23, 2.78 for HCV and 4.39, 95% CI 1.51, 12.76 for HBV/HCV coinfection].

Findings from this dissertation will inform clinical care of PLHIV in low- and middle-income countries. Our results suggest that 1) PLHIV with hyperglycemia and low BMI represent a subgroup with high risk of TB incidence, 2) PLHIV with active TB experience higher mortality and lower mean CD4 cell counts during the follow-up, and 3) hepatitis coinfection and hyperglycemia are associated with higher risk of mortality in PLHIV. We highlight in this dissertation the need for guidelines to prevent and manage TB, HBV, HCV and hyperglycemia in PLHIV.

Associations of Chronic Infectious and Non-infectious Disease Comorbidities with HIV Clinical Outcomes

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APPROVAL PAGE

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Author's Statement Page

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Chapter 1: Literature Review and Statement of Purpose

1.1 Global burden of HIV, TB, HBV/HCV and diabetes mellitus

Globally, human immune deficiency virus (HIV), tuberculosis (TB) and hepatitis B virus (HBV), hepatitis C virus (HCV) infections and type 2 diabetes mellitus (T2DM) are still significant global health burdens. Although the incidence of HIV has been declining globally over the last decade, the rate of decline is slow to meet the United Nation Sustainable Development Goal's (SDG) target to end the HIV epidemic by 2030 (<200,000 new HIV infection per year) [1,2]. Worldwide in 2018, an estimated 37.9 million people were living with HIV (PLHIV), and 1.7 million people were newly infected with HIV [3]. During the last decade, the trend of HIV-related deaths has decreased globally with the increasing access to antiretroviral therapy (ART). However, nearly a million people still died from HIV-related illnesses globally in 2017 and HIV was ranked as 8th in the leading cause of death. Moreover, declined in the incidence of HIV and HIV-related mortality is not homogeneous across countries or population. The incidence of HIV has declined slower in developing countries where HIV infections are concentrated among the key population [2]. In addition, most of the HIV-related deaths are in HIV-infected patients with comorbidities such as TB disease and other non-AIDS-related conditions [4].

Similarly, the incidence of TB disease has declined globally. However, the rate of decline still needs to accelerate to reach the End TB target of the SDG by 2030 (<10 incident TB cases per 100,000 population per year) [5]. There were 10 million incident TB cases in 2017 with 1.6 million people died from TB which is one of the top 10 causes of death worldwide. The burden of TB is not distributed equally across the world as more than 95% of the case and deaths were from developing countries and half of them were in South-east Asia and Western Pacific Region [6].

People living with HIV, those with T2DM, tobacco users and children have higher risk of TB and TB related deaths.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are another infectious disease of global concern due to their high public health burden. In 2015, estimated 240 million people had chronic HBV infection and 150 million had chronic HCV infection [7]. It is estimated that more than 686,000 people die each year from HBV infection and 700,000 from HCV infection.

While the global disease burden due to infectious diseases such as HIV and TB has declined, the disability and early mortality due to non-t diseases have increased by 40% between 1990 and 2017 [8]. One of the SDG's target is to reduce the premature mortality due to non-infectious disease by one third by 2030 [1]. T2DM is one of the primary non-infectious chronic disease and one of the leading cause of death in the world [9]. In 2016, 422 million people living with DM, of which more than 90% of them were T2DM and 1.6 million died from DM, of which 85% of them were from low- and middle-income countries.

In many low- and middle-income countries, the control of infectious disease have not yet achieved while the disease epidemic has been shifted from infectious disease to chronic non-infectious disease [10,11]. Global data shows that the prevalence of T2DM is increasing in the countries which bear the brunt of the HIV and TB epidemic [6,12,13]. Converging of infectious and non-infectious diseases in the low- and middle-income countries threatens the global progress of the control of these diseases. Hence, it is critical to understand the association and interaction between each of these diseases to optimize the screening and management of TB, HIV, HBV/HCV and T2DM to reduce disease-related morbidity and mortality.

1.2 Tuberculosis comorbidity and HIV clinical outcomes

Tuberculosis (TB) is the principal comorbidity and the leading cause of death among people living with HIV (PLHIV) [6,14–16]. Nine per cent (920,000 cases) of the incident TB cases occurred in PLHIV in 2017. Nearly one-third of a million HIV-related global deaths in 2018 were attributed to TB disease [13].

TB is the disease caused by bacteria called *Mycobacterium tuberculosis* (*Mtb*), an airborne infection transmitted through inhalation of droplets containing *Mtb.* TB is primarily a pulmonary disease but can also cause disease in extrapulmonary organs and systems. Once infected with *Mtb*, most of the host eliminate or contain the infection without symptom while some of the progress to active TB disease depending on the host innate and adaptive immune response and bacteria virulence. The former state is classified as a latent TB infection. One-third of the global population estimated to have latent TB infection which can progress or reactive to an active TB disease. Active pulmonary disease is presented by symptoms such as cough with productive sputum, fever, weight loss which can be contagious. Some of the infected people develop an active extrapulmonary TB disease in which the symptoms will depend on the sites of the disease [17,18]. Individual can advance or reverse the stages in the spectrum of TB (infection eliminated, latent TB infection, sub-clinical TB disease, active TB disease and reactivation of TB disease) depending on the host immune response and comorbidities.

In non-HIV population, the risk of reactivation from latent TB infection to active TB disease is 10% in their lifetime. However, in HIV-positive patients, the course of *Mtb* infection is altered and the lifetime risk of development or recurrence of active TB disease increase to 2 to 5 times during the early and chronic phase of infection and 20 to 37 times during the severe

immunodeficiency stage compared to the non-HIV population [19]. The incidence rate of TB disease in HIV-positive patients reported from different epidemiology studies was range from 1.9 to 9.5 TB cases per 100 person-years follow-up among those who were not on ART treatment and from 0.5 to 4.4 per 100 person-years follow-up among those on ART [20–22]. The risk of TB disease in HIV increases while the immune level decrease (clinically measured by CD4+T cell count and WHO HIV clinical staging) [23,24], and the ART is the most effective way to reduce the risk of TB disease in HIV patients by restoring the immune function [25]. However, the risk of TB disease in PLHIV on ART with normal immune level is still higher than the risk of TB disease in the non-HIV population [21].

In addition, comorbidity with TB in HIV patients increases the risk of mortality by four-fold [26]. The host-pathogen interactions involved in HIV and TB coinfection leads to unfavorable clinical outcomes in HIV/TB co-infected patients [19,27]. First, co-infection with TB promotes the rapid HIV disease progression as a result of the increase in HIV replication and propagation due to increased immune activation during the host response to TB [28–30]. Second, HIV attacked the CD4 cell and macrophages which are important for host defense against *Mtb*. HIV depletes CD4 cell which produces interferon-γ which is important for autophagic clearance of *Mtb* [31]. HIV can also infect the macrophage and inhibit the killing (phagocytosis and autophagy) of *Mtb* in the macrophages. Third, both HIV and TB diseases are considered as chronic inflammatory diseases. DNA products from HIV activate inflammasome and effector molecules from TB bacteria release pro-inflammatory cytokines resulting in cavitation and releasing of bacteria into extracellular spaces causing severe TB disease. Finally, due to the downregulation of innate immune and immunoregulatory response to TB by HIV before ART, the exaggerated inflammatory response, known as tuberculosis-associated immune reconstitution inflammatory

syndrome, occurs once the patient is initiated on ART which worsens the TB disease leading to early ART mortality [32].

Hence, TB comorbidity poses substantial challenges for HIV clinical management. HIV/TB patients experience poor clinical outcomes such as impaired in immune recovery and higher mortality [33,34]. Subclinical presentation of TB disease in HIV is also common, resulting in delayed in TB diagnosed, contributing to the increased mortality in HIV/TB patients. Signs and symptoms of TB in HIV patients are different and severe than non-HIV population [35] and the traditional diagnosis tools such as tuberculin skin test for TB infection or sputum smear microscopy for TB disease are not sensitive in HIV/TB patients leading to challenges in the management of both diseases. Although ART can reduce the risk of TB-related mortality in HIV/TB patients, several factors and mechanisms listed above contribute to increased risk of mortality among HIV/TB coinfected patients even on ART compared to infection with HIV or TB alone [28,30,33,36,37]. Most of the HIV patients (5-40%) had active TB at the first time of presenting to health facilities missing the opportunities to receive TB preventive therapy (latent TB treatment to prevent progression to or reactivation of TB disease) or ART to reduce the risk of TB disease. Hence, optimal management of HIV/TB co-infected patients is critical to lowering HIV-related mortality globally.

1.4 Hepatitis B and C virus coinfection and HIV clinical outcomes

As HIV and HBV or HCV share a common route of transmission, HIV and HBV or HCV coinfection is not uncommon. Globally, 3 to 6 million people with HIV were estimated to be co-infected with HBV and about 2.3 million people living with HIV were estimated to be co-infected with HCV in 2015 [38,39]. Studies have suggested that HIV co-infection with hepatitis B and/or

C infections increases the risk of chronic infection and liver disease, accelerates liver fibrosis and complicates the management of both infections leading to increased mortality [40–43]. However, there are some studies suggested that hepatitis C coinfection did not increase the mortality in the studies conducted before the era of highly active ART but did increase the mortality in studies included patients on ART [44]. Previous studies showed that the successful treatment of HBV and HCV together with ART can limit the liver damage and reduce mortality [45–47]. However, access to HBV and HCV treatment is very limited in low and middle-income countries and the mortality related to HBV and HCV in PLHIV could be still high.

1.3 Type 2 diabetes mellitus comorbidity and HIV clinical outcomes

T2DM is one of the types of DM characterized by the underlying pathophysiology of insulin resistance in muscle, fat and liver, insulin deficiency due to impaired insulin secretion, excessive hepatic glucose production and abnormal fat metabolism. Insulin is required for muscle and liver cells to use glucose to regulate blood glucose level. Increased adipocyte (fat cell) increases the secretion of adipokines which in turn impaired utilization of insulin by muscle and liver cell leading to hyperglycemic state. Also, products of adipocytes and adipokines increase the release of pro-inflammatory cytokines resulting in an inflammatory state that can enhance insulin resistance in adipocyte, liver and muscle. Chronic state of hyperglycemia due to T2DM can result in micro and macrovascular complications such as cardiovascular disease, blindness, end-stage renal disease, amputations, and hospitalizations. T2DM can be diagnosed by measuring blood glucose level using fasting blood glucose (FBG), oral glucose tolerance test (OGTT) or glycated haemoglobin (HbA1c) and managed the glycemic level by oral hypoglycemic drugs or injection insulin to prevent complications.

Although there are mixed results regarding higher prevalence and incidence of T2DM and hyperglycemia among HIV compared to the general population, many of the studies pointed to increase risk of T2DM among HIV patients compared to the general population [48–51]. The incidence of T2DM in HIV-positive Canadian men was reported to be 1.39 times higher than men in the general population of similar age [50]. Similarly, in the studies from Brazil and Italy, the T2DM prevalence trend was increasing in the HIV population and the risk of T2DM is higher in HIV compared to non-HIV [52,53]. Studies from Africa and Asia also found that the prevalence of DM was higher among PLHIV compared to the non-HIV population [54–57].

Persistent immune activation and chronic low-grade inflammation due to HIV infection leading to the production of inflammatory cytokines and mediators are reported mechanisms that associated with increased risk of insulin resistance and T2DM in PLHIV [58]. In addition, scaling up of ART globally during the last decade allows PLHIV increasing access to ART leading to increases in life expectancy which increase the subsequent risk of metabolic diseases that are common in general ageing population [58–64]. Furthermore, commonly used ART such as protease inhibitor and nucleoside reserve transcriptase inhibitors are associated with metabolic disturbance, change in body fat distribution, decrease insulin sensitivity and beta-cell dysfunction due to changes in mitochondria function and adipokines which can increase the risk of T2DM [65–67].

T2DM comorbidity in PLHIV increases the risk of death and common diabetes, HIV- or ART-related complications largely due to the synergism between HIV and DM [68–70]. Studies showed that DM patients with HIV had poor glycemic control and increased incidence of diabetes complications such as neuropathy and nephropathy compared to non-HIV [71,72]. One study found that DM patients with HIV compared to non-HIV had a higher risk of increased brain's

white matter hyperintensities, the condition associated with increased risk of stroke, dementia, and death [73]. In PLHIV, DM increased the risk of neurocognitive disorder and dementia in ageing HIV patients compared to those without DM [74,75]. DM found to be a risk factor for renal side effect among PLHIV on tenofovir, a commonly use ART [76,77]. In addition, DM was an independent risk factor for increased HIV-related chronic renal disease compared to those who did not have DM [78–80]. Hence, there is a need to integrate screening, prevention and management T2DM morbidity in HIV care which is not being addressed in the routine HIV clinical care in many settings [81–86].

1.4 Relationships between type 2 diabetes mellitus and tuberculosis

Epidemiological studies have shown that there is an increased co-prevalence of T2DM and TB posing challenges in TB control, especially in low- and middle-income countries [87]. The prevalence of T2DM among TB patients ranged from 1.8 to 54%, and the prevalence of TB among T2DM patients ranged from 0.1 to 36 % [88–91]. The country-level analysis done for 163 countries showed that both TB incidence and prevalence increased in countries with increased T2DM prevalence during ten years [92]. Although the risk of TB in people living with T2DM is not as high as in PLHIV, TB cases attributable to DM is higher than to HIV due to the rapid increase of T2DM epidemic worldwide [27]. The estimated population attributable fraction of TB cases due to T2DM ranged from 10% to 20%, and the estimated TB cases contributed by T2DM was 1,042,000 in 2012 [93].

T2DM increases the risk of TB disease by two- to four-fold [91]. Hyperglycemia during T2DM is associated with a dysfunctional innate and adaptive immune responses of T2DM patients to *Mtb* [94,95]. Many immunological studies using animal and human models suggested that

impairs in phagocytic activity of alveolar macrophage and delayed innate and adaptive immune responses increase the risk of TB infection, the low level of pro-inflammatory cytokines required to restrict the *Mtb* growth increases the risk of progression from TB infection to disease and the dysfunctional immunity to *Mtb* increase risk of poor TB treatment outcomes in patients with T2DM [96–99]. Some studies also suggested that underperforming innate immunity followed by a hyper-reactive cellular response to *Mtb* during TB disease might contribute to more lung tissue damage and more adverse clinical outcomes in TB patients with DM [100].

On the other hand, there is a plausible mechanism by which TB disease may increase the risk of T2DM [101,102]. Early evidence indicates that TB disease increases the risk of stress hyperglycemia, a state of transient hyperglycemia induced by the acute illness of TB disease and reversion occurs after anti-TB treatment [103–105]. Persistent systemic inflammation, pro-inflammatory cytokine signaling, and elevated stress hormones during TB disease can lead to increased insulin resistance and stress hyperglycemia, and in some patients may induce overt T2DM [101].

Most of the epidemiological studies to date examine the impact of T2DM or hyperglycemia on TB disease outcomes. Many observational studies showed that among patients with TB disease, T2DM and hyperglycemia increase the risk of poor TB treatment outcomes including delayed culture conversion, death, and relapse [97,106–109]. The findings on the risk of mortality among TB/DM patients is mixed as some studies suggested higher mortality among TB/DM patients compared to non-DM patients, [110–112] however, few studies suggested that the risk of mortality was not different or lower in TB/DM patients [106,113,114]. Nonetheless, there is strong evidence indicating that TB patients with DM experience a severe form of TB, such as more lung cavitation and hemoptysis [107–109]. In addition, T2DM is associated with unfavourable outcomes of TB

treatment as more drug-resistant TB, delayed weight gain and a lower increase in haemoglobin level were reported among TB patients with DM [112,115–118].

In contrast, there is a very few epidemiological studies examine the potential epidemiological and clinical impact of TB on the risk of T2DM although there are plausible immunometabolic mechanism that TB disease can increase the risk of hyperglycemia and T2DM [102].

1.5 Gaps of knowledge on comorbidities of TB and T2DM among PLHIV

The emerging syndemic of HIV, TB, and T2DM is further complicated due to the interaction among them. In 2013, Oni et al. highlighted the importance of synergism between three diseases and the neglected priority in research on this issue. He suggested a list of priority research including to investigate the strength of the interaction between TB and T2DM in people with HIV and to assess the potential for active screening for TB in people with T2DM and HIV [119]. Later, in 2015 and 2018, Harries et al. highlighted the emerging epidemic of these three diseases in low and middle-income countries and also called the scientific community to recognize the importance of interaction between these three diseases and accelerate the research on comorbidities. In addition, the authors suggested the integrating the care and treatment for HIV, TB and T2DM for preventing and early diagnosis of TB and DM and improving the treatment success rate and outcome of the three diseases [4,120]. Furthermore, in the research agenda addressing the converging epidemic of TB and DM by Critchley et al. in 2017, the research to address interactions between TB, DM and HIV was included as an important priority because there was a growing epidemic of DM in sub-Saharan countries where the prevalence of HIV was high [121].

However, there are limited numbers of research that studied these three diseases together and little is known about the strength, casual direction and mechanism of association between T2DM and TB among PLHIV. We conducted a literature search in PubMed, Google Scholar and the Cochrane Systematic Review using the search term “tuberculosis AND HIV AND [diabetes mellitus OR hyperglycemia]” and found 334 articles from the database search. After screening the abstracts, there were only 24 articles that discussed or studies on these three diseases together. Among them, three articles are review articles, 12 articles are research studies with the primary aim to examine the association between TB and DM in the general population and reported the association in HIV as a subgroup analysis and nine articles are research studies with the primary aim to assess the association between TB and DM in PLHIV or TB, DM and HIV together. Among 21 research articles, three of them are systematic reviews and 18 studies are original research (**table 1)**. Hence, there is a major knowledge gap remain regarding the interaction between TB, T2DM and HIV.

Most of the studies were cross-sectional studies to determine the association between TB and DM among HIV patients. Hence, the causal direction between DM and TB cannot be determined from the association observed. All the studies interpreted the observed association as DM is a predictor for the increased risk of TB among HIV patients based on the already known causal association among the non-HIV population which is DM as a host risk factor for TB disease. However, there has been increasing evidence of a plausible mechanism that TB disease may lead to stress hyperglycemia and increase the risk of DM. None of the studies can determine this reverse direction due to methodological limitation except the study conducted by Faurholt-Jepsen et al., which included C-reactive protein measurement as a proxy for acute phase response and adjusted for the possibility of stress-induced hyperglycemia due to TB. In addition, the observed

relationship between DM and TB among HIV from these studies were heterogeneous due to heterogeneity in measurement of the exposure and the outcome.

Among 18 original research, three studies using longitudinal cohort data. The prospective cohort study conducted by Achhra at el., assess the association of incidence of TB with DM and glycemic level among HIV patients. DM was defined by using FBG. However, the authors acknowledge that not all measurements were FBG due to the study sites' patient standard of care. The authors also addressed confounders by including in adjusted model except smoking which was an important factor associated with both TB and DM.

The second study, a retrospective cohort study conducted by Moreira et al., assess the effect of hyperglycemia during TB treatment on TB treatment outcome and 1-year mortality among HIV/TB patients. Hyperglycemia was defined using FBG measured at two times during TB treatment. The findings showed that patients with hyperglycemia had a higher risk of adverse TB treatment outcome and mortality (adjusted HR: 3.7, 95%CI: 2.2-6.8). However, possible confounders such as ART use, smoking, BMI were not included in the adjusted model. The authors also analyzed the changes of the glycemic level after 36 months of mean follow up (SD: 24 months) and found that 22 patients out of 49 hyperglycemic patients during TB treatment developed DM while one of 414 euglycemic developed DM.

The third study was a retrospective cohort study which we conducted in Myanmar to assess the association between hyperglycemia at enrollment and risk of all-cause mortality in PLHIV and whether the relationship is differed by TB status. We found that there was an interaction between hyperglycemia and TB on the risk of mortality in PLHIV. In TB patients, hyperglycemia was not a significant risk factor for mortality (adjusted HR, 1.0; 95% CI, 0.8–1.2) although hyperglycemia

was a risk factor for mortality among non-TB patients. As the study used RBG as a measure of hyperglycemia and no information on DM status and DM medications, there was a risk of measurement bias and there is no clear conclusion can be drawn how TB and DM or hyperglycemia interact in HIV patient.

According to our systematic literature search, there is not enough study to conclude the strength of association, causal relationship and interaction between TB and T2DM among HIV patients. In addition, evidence regarding the role of TB-induced hyperglycemia in PLHIV is critically missing. Furthermore, a limited number of longitudinal studies to assess the role of T2DM and hyperglycemia on the clinical outcome of TB and HIV. Hence, empirical evidence for the management of T2DM and hyperglycemia in patients with TB/HIV is lacking, and more research is urgently needed to reduce the risk of mortality in HIV/TB patients comorbid with hyperglycemia and T2DM.

1.6 Gaps of knowledge on comorbidities of HBV/HCV and T2DM in PLHIV

There are studies suggesting that HCV co-infection significantly increased the risk of T2DM especially in HIV patients with HCV viremia [122,123]. Underlying mechanism of increased risk of T2DM in patients with HCV include the extrahepatic effects of HCV infection on endocrine, HCV replication in extrahepatic cells, a heightened immune reaction with systemic effects or the HCV treatment causing insulin resistance and hyperglycemia [123–126]. Comorbidity with HCV and T2DM also increased risk of cardiovascular events and deaths [127]. Studies also suggested that successful HCV therapy decreased the adverse outcomes and mortality related to T2DM in patients with HCV [128]. However, there is no information on the risk of mortality related to HBV and T2DM or hyperglycemia in HIV population.

1.7 Statement of purpose

The overall goal of this dissertation is to support the understanding of the association between chronic infectious - TB, HBV and HCV coinfection, and non-infectious disease - T2DM comorbidities on the HIV clinical outcomes. To achieve this goal, the following three observational studies were conducted in a cohort of PLHIV in Myanmar, a country which has a high burden of all the diseases mentioned. Like in many resource-limited and high HIV burden countries, gold standard T2DM screening using glycated hemoglobin or fasting blood glucose is not implemented in Myanmar due to limited resources. However, random blood glucose is usually measured at enrollment to HIV care and we used random blood glucose measurement as a proxy to the glycemic level of patients.

Study 1 assessed the biological interaction between low BMI and hyperglycemia with the risk of TB disease in PLHIV. This study will help to identify the high-risk group of TB disease in PLHIV to target public health and clinical interventions to effectively use limited resources to reduce the TB burden in PLHIV.

Study 2 estimated the association between active TB with all-cause mortality, change in CD4 cells and virological failure after one year on ART and also assessed whether blood glucose level mediates the association between active TB and all-cause mortality among PLHIV. While there is a growing knowledge of mechanism of association between TB and hyperglycemia with mortality in general population, this study presents the finding from HIV population.

Study 3 examined the association between HBV and HCV coinfection with all-cause mortality in PLHIV and whether the association between HBV and HCV coinfection with all-cause mortality in PLHIV varied by hyperglycaemia status. This study will inform the excess risk

of mortality due to hepatitis B and C coinfection and hyperglycemia. To date, there is no information on association between HBV and/or HCV and hyperglycemia with mortality in PLHIV. Collectively, the three studies presented in this dissertation will contribute new knowledge to inform the clinical and public health guideline for prevention, screening, diagnosis and management of comorbidities in PLHIV to reduce mortality.

Table 1: Summary of studies that report findings on HIV, TB and T2DM or hyperglycemia together

	Title of the study	Year of study	Objectives	Study design	Study population and sample size	Outcomes	Results
1	Tuberculosis and diabetes in Guyana[129]	2011	To estimate the prevalence of DM in TB	Cross-sectional	100 TB patients	DM measured by RBG	14% of TB patients had DM, and none of the DM patients had HIV.
2	Diabetes is a Risk Factor for Pulmonary Tuberculosis: A Case-Control Study from Mwanza, Tanzania[130]	2006-2009	To assess the association between diabetes and TB and the role of HIV as an effect modifier,	Case-control	803 TB cases and 350 non-TB neighbourhood control	DM measured by FBG, OGTT	After adjusting for potential confounders, there was an association between TB and DM (aOR: 4.2, 95% CI: 1.5-11.6) but the association between TB and DM was not observed in HIV infected patients (aOR: 0.1, 95% CI: 0.01-1.8).
3	Important co-morbidity in patients with diabetes mellitus in three clinics in Western Kenya[131]	2007-2011	To determine the prevalence of DM patients with a history of TB and HIV	Cross-sectional	1376 DM patients	TB and HIV	33 (2%) patients had a history of TB before DM diagnosis and 44 (3%) had TB after DM diagnosis. Among 44 DM patients who had TB, 5(17%) were HIV positive and TB/ DM/HIV comorbidity was 1%.
4	Overt diabetes mellitus among newly diagnosed Ugandan tuberculosis patients: a cross-sectional study[132]	2011-2012	To determine the prevalence of DM among TB patients	Cross-sectional	260 TB patients	DM measured by FBS	208 patients were HIV co-infected. DM prevalence among TB was 8.5% (22 patients). In adjusted analysis, HIV coinfected patients had lower odds of having DM (OR=0.17, 95% CI 0.06-0.51).

5	Relationship between hyperglycemia and the risk of tuberculosis in Asian HIV positive individuals in the antiretroviral therapy era: cohort study[133]	2005-2010	To determine the relationship between glycemic level (FBG) and TB in HIV	Prospective cohort	4,617 HIV patients	TB disease	TB incidence was 1.58/100 person-years There was a higher risk of TB among DM patients compared to non-DM (Adjusted HR:1.34 (IQR 1.01-1.79)).
6	Screening for diabetes mellitus and human immunodeficiency virus infection in persons with tuberculosis[134]	2010-2012	To determine the prevalence of DM and HIV in TB patients	Cross-sectional	3,376 TB patients	DM and HIV	The prevalence of DM was 4.8 % and HIV was 3.5%. The prevalence of HIV/DM comorbidity in TB patients was 0.3%.
7	Treatment Outcomes in Tuberculosis Patients with Diabetes: A Polytomous Analysis Using Brazilian Surveillance System[135]	2001-2011	To assess the factors influencing the outcome of TB-DM patients	Analysis of the result of a surveillance system	26,401 TB-DM patients	Loss to follow up and death	The odds of loss to follow up and death were higher in HIV/AIDS patients (OR=2.16 and 2.87 respectively)
8	Opportunistic Infections among People Living with HIV (PLHIV) with Diabetes Mellitus (DM) Attending a Tertiary Care Hospital in Coastal City of South India[136]	2011-2012	To assess common opportunistic infections among HIV/DM patients	Case-control	37 PLHIV with DM as cases and 37 PLHIV without DM as control	Pulmonary and extrapulmonary TB disease	Prevalence of TB was not significantly different between PLHIV-DM and PLHIV without DM (Extrapulmonary TB:22% in PLHIV-DM and 34.5% in PLHIV, Pulmonary TB: 16% in both group).
9	Factors associated with diabetes mellitus among adults with tuberculosis in a	2000-2013	To assess the factor associated with prevalence DM among TB	Cross-sectional	5849 TB patients	Prevalence of DM	Prevalence of DM was 5.9%.

	large European city, 2000–2013[137]						HIV patients had lower odds of having DM (adjusted OR: 0.27 (95% CI: 0.10-0.57).
10	The diabetes-tuberculosis co-epidemic: the role of international migration[138]	2007-2012	To assess the factor associated with DM among TB	Retrospective cohort	971 TB patients	Prevalence of DM diagnosed using WHO criteria	DM was diagnosed in 48 patients (5%) before their TB diagnosis and 15 (2%) during admission for TB treatment. Patients with HIV had lower odds of having DM in TB patients (OR: 0.2 (95% CI: 0.0-0.8)
11.	Transient Hyperglycemia in Patients with Tuberculosis in Tanzania: Implications for Diabetes Screening Algorithms[104]	2012-2014	To compared DM screening strategies	Case-control	378 TB cases and 491 non-TB control cases	Diagnosed DM and hyperglycemia using FBG, OGTT and HbA1c	Higher odds of DM among TB (OR:6.5, 95% CI: (3.3-12.9). Stratified by HIV: the OR among HIV negative was 19.3 and among HIV infected was 4.7 showing association is weaker in HIV patients (only if measured by HbA1c)
12	Tuberculosis and diabetes in Nigerian patients with and without HIV[139]	2017 (Published)	To determine the prevalence of DM among TB with or without HIV	Cross-sectional	410 hospitalized presumptive TB patients	TB and DM measured by FBG and HbA1c	62 (15%) of 113 TB patients had DM. HIV negative DM patients had a higher risk of TB than HIV positive DM patients (aOR 4.3 vs 3.3).
13	The change in blood glucose levels in tuberculosis patients before and during anti-tuberculosis treatment in China[140]	2015	To understand if blood glucose levels were stable or fluctuated during anti-TB treatment	Prospective cohort	270 patients on anti-TB treatment	FBG	Patients with HIV had unstable blood glucose level during anti-TB treatment

14	Trilateral overlap of tuberculosis, diabetes and HIV-1 in a high-burden African setting: implications for TB control[141]	2013-2015	To determine the association between TB and diabetes/impaired glucose regulation in the context of HIV-1	Cross-sectional	852 patients with respiratory symptom	DM measured by FBG and HbA1c and TB	The prevalence of DM among 414 TB patients was 12.6% and among 438 non-TB patients was 10.1%. In adjusted analysis, diabetes was associated with TB (OR:2.4 (95% CI: 1.3-4.3). Heterogeneity of association was found once stratified by HIV status but the association between DM and TB was still strong in HIV-positive patients.
15	The prevalence and determinants of active tuberculosis among diabetes patients in Cape Town, South Africa, a high HIV/TB burden setting[142]	2014-2015	To investigate the prevalence of active TB among DM	Cross-sectional	440 DM patients	Active TB	Active TB prevalence was 3%. There was no significant difference in glycemic level between TB patients and non-TB cases. HIV was a significant risk factor associated with active TB (aOR:11.3, 95% CI: 3.26-39.42).
16	Hyperglycemia during tuberculosis treatment increases morbidity and mortality in a contemporary cohort of HIV-infected patients in Rio de Janeiro, Brazil[143]	2010-2015	To assess the prevalence of hyperglycemia among HIV/TB patients on anti-TB treatment and compare the TB treatment outcome and 1-year mortality rate according to the glycemic status of patients during TB treatment.	Retrospective cohort	473 HIV/TB patients	DM and hyperglycemia measured by FBG, TB treatment outcome and 1-year mortality rate	Prevalence of hyperglycemia was 10% and known DM was 2%. The 1-year mortality rate was significantly higher in hyperglycemic patients (aHR: 3.72, 95% CI: 2.17-6.38).

17	Synergism between diabetes and human immunodeficiency virus in increasing the risk of tuberculosis[144]	2015-1016	To study the synergism between DM and HIV in increasing the risk of TB symptoms	Cross-sectional	7,708	HIV (self-reported or tested), DM measured by RBG and TB symptoms	DM and HIV patients had a higher risk of TB symptoms (aOR 1.36, 95%CI 1.11–1.67 and aOR 1.66, 95%CI 1.40–1.97 respectively). There was an interaction between HIV and DM on the multiplicative scale.
18	Hyperglycemia and risk of all-cause mortality among people living with HIV with and without tuberculosis disease in Myanmar (2011–2017)[145]	2011-2017	To assess the association between hyperglycemia at enrollment and risk of all-cause mortality in PLHIV and whether the the relationship is differed by TB status	Retrospective cohort	25,851 HIV patients	Hyperglycemia measured by RBG at enrollment) and all-cause mortality	Hyperglycemic patients had a higher risk of mortality (adjusted HR, 1.1; 95% CI, 1.0–1.3). There was an interaction between hyperglycemia and TB in association with mortality. In TB patients, hyperglycemia was not a significant risk factor for mortality (adjusted HR, 1.0; 95% CI, 0.8–1.2).

TB: tuberculosis; DM: diabetes mellitus; RBG: Radom blood glucose; FBS: Fasting blood glucose; OGTT: oral glucose tolerance test; OR odds ratio; aOR: adjusted OR; HR: hazard ratio; aHR: adjusted HR;

Chapter 2: Paper 1- Association between low body mass index and hyperglycemia with the risk of TB among people living with HIV (In progress)

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ABSTRACT

Background

Low body mass index (BMI) and hyperglycemia are each establish risk factors for tuberculosis (TB) disease among people living with HIV (PLHIV); however, there is limited understanding how these factors interact. We estimated biological interaction between low BMI and hyperglycemia with the risk of TB disease among PLHIV.

Methods

PLHIV (≥15 years old) who had records of random blood glucose (RBG), weight and height measurements at enrollment to Integrated HIV Care Program, Myanmar, 2011-2017 were eligible. Exclusion criteria were receiving TB treatment before enrollment or receiving isoniazid TB preventive therapy or multi-drug resistant TB treatment during follow-up. The outcome was incident TB, defined as patients starting first-line TB treatment during follow-up. We used Cox proportional models to estimate the interaction between low BMI (BMI ≥18.5 kg/m2) and hyperglycemia (RBG ≥140 mg/dl) on the risk of TB disease.

Results

Among 41,179 PLHIV enrolled, 20,865 patients met eligibility criteria. The median age was 36 years (range 15-91 years), 55% were male, 36% had low BMI, 6% had hyperglycemia. During the median follow-up of 2.2 years (IQR: 0.5,4.2), the incidence of TB was 6.7 per 100 person-years. Patients with low BMI or hyperglycemia had a higher hazard rate of TB compared to their counterpart [adjusted HR (aHR): 1.41 (95% CI: 1.32, 1.51) and 1.17 (95% CI: 1.03, 1.32), respectively]. In interaction analysis, patients with joint exposure to low BMI and hyperglycemia

had the highest hazard rate of incident TB compared to those with no exposure [aHR: 1.84 (95% CI: 1.55, 2.18)] and the relative excess risk (of TB disease) due to the interaction of two exposures was 0.42 (95% CI:0.07,0.78).

Conclusions

PLHIV with low BMI and hyperglycemia represent a subgroup with high risk of TB incidence. There is a need to assess if TB preventive treatment, nutritional support, and hyperglycemia management can reduce TB incidence in this joint exposed group.

BACKGROUND

Among people living with Human Immunodeficiency Virus (PLHIV), tuberculosis (TB) disease is a major opportunistic infection and the leading cause of death. Globally, 251,000 deaths among PLHIV in 2018 were attributed to TB disease [146]. Comorbidity with TB disease poses substantial challenges in the clinical management of HIV and threatens the global public health goals of reducing morbidity and mortality among PLHIV [33,34]. Most of the countries affected by the dual burden of TB and HIV are resource-limited countries. Therefore, identification of subgroups to target public health and clinical interventions is urgently needed to effectively use the limited resource to reduce the TB burden among PLHIV.

Low BMI (BMI <18.5 kg/m^2) is a known risk factors for TB disease in PLHIV [147–149]. Another factor associated with increased risk of TB disease is type 2 diabetes mellitus (T2DM) and hyperglycemia (high glycemic level in people with or without T2DM) [133,150]. To date, most data regarding hyperglycemia and TB risk come from patients without HIV [150–152]. Low BMI and hyperglycemia are common in PLHIV [57,153–155]. About 30% of PLHIV in resource-limited countries were low BMI [20,156]. About 20% of PLHIV were reported to be hyperglycemia (fasting blood glucose >110mg/dl) [57]. Therefore, it is important to understand and assess the biological interaction between low BMI and hyperglycemia in PLHIV to identify the subgroup with increased risk of TB disease to target interventions that could reduce risk of TB disease among them.

To determine the subgroup, biological interaction between the two risk factors can be measured by partitioning the risk among those with joint exposure from those with exposure to either risk factor separately [157,158]. The joint effect of BMI and T2DM on TB disease in non-HIV population had been studied in different settings [159–161]. All the studies showed that there

was a joint effect of BMI and T2DM on the risk of TB disease, although the direction of the associations was contradicting among studies. A cross-sectional study from India found that the highest risk of TB disease was observed among participants with overweight or obese and T2DM compared to those without diabetes with normal weight [159]. However, a cohort study from Taiwan showed that underweight individual with T2DM had a higher risk of TB disease compared to an individual with normal weight and without T2DM [160]. Similarly, a recent study from Singapore showed that underweight individuals with T2DM had the highest risk of TB disease compared to an obese individual with diabetes mellitus [161]. We can make an inference from the latter two studies that underweight and T2DM may have synergistic interaction on the risk of TB disease.

To date, there is a lack of information regarding the interaction between low BMI and hyperglycemia among PLHIV. In many resource-limited and high HIV burden countries, gold standard T2DM screening and glycemic level measurement using glycated hemoglobin or fasting blood glucose is not implemented due to limited resources. However, random blood glucose is usually measured at enrollment (the time of entry to HIV care) or at the start of antiretroviral therapy (ART) which can be used as a proxy to the glycemic level of patients. Therefore, we aimed to assess the biological interaction between low BMI and hyperglycemia at enrollment on the risk of TB disease among PLHIV from Myanmar.

METHODS

Study Design

This was a cohort study using secondary program data.

Study Setting, sources of data and data collection

Myanmar, with a population of 52 million, is one of the 30 high tuberculosis burden countries. Tuberculosis and HIV remain two major public health problems in Myanmar. In 2018, there were 212,000 PLHIV in Myanmar and the TB incidence was 338/100,000 population with about 15,000 people co-infected with TB and HIV [3,146].

The country office of the International Union Against Tuberculosis and Lung Disease (a non-governmental organization) and the National AIDS Program (NAP) are jointly implementing Integrated HIV Care Program for providing HIV treatment and care to PLHIV in the public health sector in 5 regions of the 15 regions of the country. In 2018, there were 49 HIV clinics under the program. The details of the services provided at the HIV clinics under the IHC program were described in detail elsewhere [162].

All PLHIV enrolled for HIV care in the clinics receive weight, height, random blood glucose (RBG), CD4 count, hemoglobin measurement and TB disease screening. They also receive screening of TB disease during quarterly follow-up visits. Patient outcomes were recorded as regular follow-up (attending clinic appointment regularly), death (patient's family or the outreach workers reported to the clinic that the patient had died), lost to follow-up (not attending the clinic within three months after the scheduled appointment date) and transferred out (patient was transferred out to other HIV care program). Date of death was recorded from hospital records if patients died at the hospital or as reported by families if the patient died at home. At every visit, patients' data were recorded on paper-based patient medical records by medical officers and entered into an electronic database by data entry operators. For this study, data of patients who

enrolled between January 2011 and August 2017 with their follow-up and outcome data until 31st August 2018 were extracted from the electronic database.

Study population

PLHIV ≥15 years who enrolled to Integrated HIV Care Program between January 2011 and August 2017 and who had records of RBG, weight and height measurements at enrollment were eligible. Exclusion criteria were age younger than 15 years, receiving TB treatment before enrollment or receiving isoniazid TB preventive therapy or treatment for multi-drug resistant TB during follow-up and not having a record of enrollment random blood glucose, weight and height measurements.

Data variables

The first exposure of interest in this study was BMI at enrollment calculated from enrollment weight and height. Patients with BMI <18.5 kg/m^2 are categorized as low BMI or underweight, 18.5–23 kg/m^2 as normal, 23–27.5 kg/m^2 as overweight and >27.5 kg/m^2 as obese as per WHO guideline [163]. The BMI was also categorized into low BMI (<18.5 kg/m2) and normal/high BMI (≥18.5 kg/m2) groups.

The second exposure of interest was an RBG level measured by glucometer using capillary blood at enrollment. RBG ≥140 mg/dl measured at enrollment was defined as hyperglycemia according to previous studies and WHO 2-hour postprandial blood glucose classification for diagnosis of prediabetes [164–166]. RBG level was also categorized into four categories <110, 100-139, 140-199 and >199 mg/dl.

The outcome of interest was incident TB. Incident TB was defined if the patient was on TB treatment (either for pulmonary or extra-pulmonary) between the date of enrollment and date of death, loss to follow-up, transferred out or of end of study (31st August 2018). TB disease was diagnosed in this setting using sputum smear microscopy, X-pert MTB/Rif assay and/or chest X-ray if the patient has any TB disease symptoms. TB disease was also diagnosed clinically when the patients had symptoms suggestive of TB even if the diagnostic investigations were negative. All the diagnosed TB patients were immediately treated unless they died or were lost to follow-up.

Covariates included age, sex, marital status, employment, literacy status (literate or illiterate), alcohol consumption (never, weekly or daily), ART status, weight, height, hepatitis B surface antigen, anti-hepatitis C antibody, baseline CD4 cell count (cells/mm^3) and anemia measured at enrollment. Anemia was categorized based on hemoglobin levels: normal (male, ≥13 g/dl; female, ≥12 g/dl), mild (male, 11–12.9 g/dl; female, 11–11.9 g/dl), moderate (both sexes, 8.0–10.9 g/dl) and severe anemia (both sexes <8.0 g/dl).

Analysis and statistics

Enrolment characteristics of patients were compared between eligible and excluded group and across BMI categories using Chi-square test. Rate of TB disease during the follow-up was calculated by dividing the number of TB cases by person-years follow-up. Person-years of follow-up was calculated from the date of enrolment to the date of TB treatment initiation, death, lost to follow-up, transferred out or 31st August 2018 (censor date). Cox proportional hazard models were used to estimate the hazard ratios and 95% confidence interval (CI) to determine factors associated with incident TB. Nelson-Aalen cumulative hazard estimates were used to plot the cumulative

hazard of incident TB during follow-up, stratified by BMI categories and hyperglycaemia status. We fitted models using BMI and blood glucose level as a continuous predictor, a categorical predictor and a restricted cubic spline with 4 knots. Proportional hazard assumption was checked using log-log survival curve, and goodness-of-fit was assessed using Schoenfeld residuals. To assess interaction, we calculated the rate of TB, incidence rate differences and the adjusted hazard ratio for each exposure level. We controlled potential cofounders for both exposures based on bivariable analysis and directed acyclic graph theory. Then, we estimated the relative excess risk due to interaction (RERI), the attributable proportion due to interaction and synergy index along with their 95% CI using the icp command in STATA [157,158]. With the assumptions that both exposures have positive monotonic effects, i.e. they are never preventive for any individual, and cofounders are controlled for both exposures, RERI >0 indicates that there is a biological interaction, an excess risk of disease due to the interaction between two exposures [158] . Attributable proportion measures the proportion of disease in the joint exposure group due to biological interaction between the two conditions. Synergy index >1 indicates that there is a biological interaction between two conditions.

We also performed sensitivity analyses. First, as smoking status was an unmeasured confounder, e-values were estimated to assess the minimum strength of the association that the smoking status would need to have with both the exposure and the outcome to shift the estimate to null [167]. We also calculated the adjusted hazard ratio using different strength of association between smoking and each exposure [168]. Second, to assess bias due to exposure misclassification, we calculated the relative risk of TB disease associated with each exposure using different sensitivity and specificity of the measurement [168]. Third, patients diagnosed with TB during the first three months of enrolment can be those who already had TB disease at enrolment

(prevalent TB). Hence, we also fit the models after excluding patients with TB disease diagnosed within three months of enrolment. Finally, patients who died or were lost to follow-up before the event (incident TB) could be a competing risk. Hence, we estimated adjusted hazard ratio using a cause-specific model as well as a sub-distribution hazard model. STATA (version 14 Stata Corp LP USA) was used for all analyses.

Ethical considerations

The study proposal was approved by the Union Ethics Advisory Group (Paris, France), Ethics Review Committee at the Department of Medical Research, Ministry of Health and Sports (Yangon, Myanmar) and Institutional Review Board at Georgia State University (Atlanta, USA). Permission to conduct the study was also obtained from The National Tuberculosis and HIV/AIDS Program, Department of Public Health, Ministry of Health and Sports Myanmar

RESULTS

Of 41,179 PLHIV enrolled during the study period, 20,865 PLHIV met inclusion criteria and were included in this analysis (**Supplemental Figure 1**). Enrollment characteristics between patients included and those excluded in the study were presented in **Supplemental Table 1**. The median age (interquartile range (IQR)) of the study cohort was 36 (30-42) years, 55% were male, 1,324 (6%) had hyperglycemia, 7,610 (37%) had low BMI at enrollment. Notably, patients older than 45 years, male, patients with CD4<200 cells/mm^3 and those with severe anemia disproportionately had low BMI at enrollment **Supplemental Table 2**. More patients in the hyperglycemic group (9%) were obese compared to the euglycemic group (7%).

Patient characteristics associated with risk of TB disease

The median (IQR) follow up duration of the cohort was 2.2 (0.5-4.2) years contributed to 53,880 person-years of follow-up and 17% (n=3,628) developed active TB during the follow-up. The incidence rate of TB was 6.7 TB cases per 100 person-years [95% CI: 6.5, 7.0]. The factors associated with active TB are presented in **Table 1**. Patients who were male [HR:1.75, (95%CI:1.63,1.88)], 25 to 45 years old [HR:1.43 (95% CI: :1.25,1.64)] or >45 years old [HR:1.39 (95% CI:1.19,1.63)] or underweight [HR: 1.97 (95% CI: 1.83,2.11)] or had hyperglycemia [HR:1.22 (1.08,1.39)] had a higher risk of TB disease. Other risk factors for TB disease included history of alcohol drinking, lower CD4 cell count, WHO clinical staging 3 or 4 and having anemia. Being on ART prior to enrollment was associated with a lower risk of TB disease [HR:0.30 (95% CI:0.23,0.40)].

Risk of TB disease by body mass index and glycemic status

The estimated cumulative incidence of active TB was highest in patients with low BMI in both glycemic levels **(Figure 1.a and 1.b)**. The differences in the incidence rate of active TB between patients with low BMI and those with BMI (≥18.5 kg/m^2) were shown in **Table 2**. One unit increase in BMI reduced the hazard rate of TB disease by 3% [aHR 0.97 [95% CI: 0.96, 0.98]. When BMI was included as a dichotomous predictor in the model, the aHR was 1.41 [95% CI: 1.32, 1.51] in patients with low BMI compared to those with normal or high BMI. When BMI was included as a restricted cubic spline in the model, aHR was 1.30 [95% CI: 1.19, 1.42] in patients with BMI 18.5 kg/m^2 compared to patients with BMI 23 kg/m^2. The estimated HR of incident TB using the restricted cubic spline regression was plotted across BMI in **Supplemental Figure 2.a.**

The differences in incidence rate of active TB between different glycemic level was shown in **Table 2**. The adjusted hazard of risk of TB disease was 1.17 [95% CI: 1.03, 1.32] in hyperglycemic patients compared to patients with euglycemic level. When blood glucose level was included as a restricted cubic spline in the model, the adjusted hazard of risk of TB disease was 1.05 [95% CI: 1.00, 1.10] in patients with blood glucose level 140 mg/dl compared to patients with blood glucose 110 mg/dl. The estimated hazard ratio of the risk of TB using the restricted cubic spline regression was plotted across blood glucose level in **Supplemental Figure 2.b.**

Biological interaction between low BMI and hyperglycemia

The rates of TB disease and adjusted hazard ratios of each dichotomous exposure level of low BMI and hyperglycemia were presented in **Table 3**. Patients with low BMI and hyperglycemia had the highest risk of active TB compared to those with BMI ≥18.5 kg/m^2 and RBG <140 mg/dl [adjusted HR: 1.84 (95% CI:1.55, 2.18)].

RERI was 0.42 (95% CI:0.07,0.78), the attributable proportion was 0.23 (95% CI: 0.06, 0.36) and synergy index was 2.01 (95% CI: 1.09, 3.74) using the adjusted hazard ratios from the above model. As both low BMI and hyperglycemia was associated with increased risk of TB disease (positive monotonic effects) and assuming all the potential confounders were controlled for both exposures, the RERI >0 and synergy index >1 indicate that there is a biological interaction between low BMI and hyperglycemia on the risk of TB disease.

DISCUSSION

Identification of subgroups with a high risk of TB disease is important to effectively allocate the public health resources to target the intervention to reduce the TB-related morbidity and mortality in PLHIV. To our knowledge, this is the first study to identify the subgroup with a high risk of TB disease among PLHIV by assessing the biological interaction between low BMI and hyperglycemia by partitioning the effect by each exposure level. Our study suggests that patients who were simultaneously underweight and hyperglycemic had a relative excess risk of TB due to joint exposure compared to exposure to either condition alone. The estimated risk of TB disease in patients with joint exposure to low BMI and hyperglycemia was 2.7 times higher compared to those who did not have any exposure. The risk in underweight patients with normal glycemia was 1.7 compared to those who did not have any exposure. We also found that the attributable proportion of TB disease due to biological interaction or joint exposure was 33%. Other important findings include more than one-third of the PLHIV had low BMI at the time of enrollment and habitual alcohol drinkers were more likely to have low BMI and had a higher risk of TB diseases.

Our results are similar to studies conducted in the non-HIV population in Asia setting. The study conducted in Taiwan by Lin et al. showed that there was a joint effect of BMI and T2DM on the risk of TB disease [160]. Of two prospective cohort included in their study, the result from one of the cohorts showed that participants who were underweight and had diabetes had the highest risk of TB compared to other levels of exposures. However, this joint effect was not detected in the other cohort included in the study. One of the limitations of their finding was that weight, height and T2DM status were ascertained from self-reported information. Another recently published study from Singapore also showed a very high risk of TB disease among underweight

individuals with T2DM compared to obese without T2DM (adjusted HR:8.3). Similarly, the Singapore study also used self-reported information for exposure ascertainment.

On the contrary, the cross-sectional study conducted in India by Kubiak et al. showed that individuals with T2DM and obesity had the highest prevalence of TB disease compared to people without T2DM and normal weight (adjusted prevalent ratio: 12.0) [159]. In their study, the adjusted prevalence ratios were similar between individuals who were underweight with T2DM and those who were in low BMI group with no T2DM. This contradicting finding can be in part explained by the difference in study design and the definition of T2DM exposure. Although the previous studies assess the joint effect of BMI and T2DM on the risk of TB, none of them calculated the quantitative measure for biological interaction such as RERI and attributable proportion due to joint exposure.

Similar to many resource-limited high HIV and TB burden countries, a substantial number (36%) of PLHIV in our cohort had low BMI at the time of enrollment. Many of the cohort studies from Asia and Africa reported that the proportion of adult PLHIV with underweight was about 28-34% [156,169–171]. Improving access to ART globally over the last decades shift PLHIV being underweight to a healthy weight as a result of starting ART earlier, preventing opportunistic infections and better immune recovery. However, PLHIV from many developing countries present to the health system late due to stigma and other factors related to socioeconomic status. A study from Uganda showed that food assistance improved BMI and reduced the proportion of underweight among PLHIV over the 12 months [172]. As underweight is a proxy for poor nutritional status, intervention such as nutritional supplementation and food security program for PLHIV should be considered in those setting in addition to early HIV diagnosis and ART [173].

One of the strengths of the study is having a large sample size with adequate follow-up time providing the opportunity to assess the risk of TB disease and allow us to make inference on the temporal association between hyperglycemia and underweight at enrollment and TB disease during follow-up. Exposure and outcome measures were relatively robust as we used the clinical data where random blood glucose, weight and height were measured by the clinic staffs and records in the individual medical record. We controlled for important confounders for exposures and outcome association such as age, sex, CD4 cell and ART status.

Limitations of the study include potential exposure misclassification as we used random blood glucose measurement to define hyperglycemia which has limited validity than fasting blood glucose measurement. We calculated relative risks (RR) of risk of TB associated with hyperglycemia using sensitivity and specificity of hyperglycemia measurement range from .80 to .99. The observed RR of risk of TB among patients with hyperglycemia was 1.51. From the sensitivity analysis, the point estimate for RR range from 0.15 to 3.07. Another limitation is that there is no information on diabetes diagnosis and treatment after the random blood glucose measurement and during the follow-up. There could be patients who were on anti-diabetes medications and successfully controlled their glycemic level which could shift over observed associated toward or away from null.

In addition, we did not have data on cigarette smoking history which is a known risk factor for T2DM and TB disease. To address this unmeasured cofounder, we calculated e-value and estimated the range of hazard ratios using different bias parameters. The e-value for the association between low BMI and risk of TB is 1.82 and e-value for the association between hyperglycemia and risk of TB was 1.64 showing that only if there is a strong association between unmeasured

confounder (smoking) and both exposure and outcome could shift our observed association toward null.

Another limitation is the potential selection bias as about 50% of the patients enrolled during the study period did not have blood glucose, weight and height measurement were excluded from the analysis. However, the demographic and clinical characteristics of patients who were included and those who were excluded from the analysis are similar and we believe that our observed estimates are generalizable.

Despite the limitations, our study results have many public health and clinical implications. First, we identified the PLHIV subgroup which has the highest risk of TB disease. As Myanmar is a resource-limited country, intervention to prevent TB disease such as providing isoniazid therapy can be considered to prioritize in the group with the highest risk. In addition, there is a need to assess if interventions such as providing a nutritional supplementation to improve weight gain and optimal control of hyperglycemia and T2DM can reduce TB incidence in PLHIV especially among joint exposure group. Finally, as habitual alcohol consumption was associated with underweight and risk of TB disease, counselling to sober alcohol use may benefit for the patients in preventing adverse clinical outcomes.

CONCLUSIONS

This study identified the biological interaction between low BMI and hyperglycemia on the risk of TB disease among PLHIV and the subgroup with joint exposure to prioritize the intervention to reduce the risk of TB disease. Both low BMI and hyperglycemia were associated with the risk of TB disease. Patients who simultaneously had low BMI and hyperglycemia

experienced about 23% excess risk due to joint exposure than those who had low BMI or hyperglycemia alone. The results highlight to consider the implementation of TB preventive therapy, nutritional supplement intervention and screening of hyperglycemia and T2DM among PLHIV and if the resource-limited, the interventions should be prioritized for joint exposure group.

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Table 1. Patient characteristics associated with incident TB among people living with HIV enrolled Integrated HIV Care Program, 2011-2017, Myanmar

		Person-years	Incident TB	IR [95% CI]	HR [95% CI]
Characteristics*	Total	53880	3628	6.7 [6.5,7.0]	
Age (year)	<25	4065	215	5.3 [4.6,6.0]	ref
	25-45	41929	2848	6.8 [6.5,7.0]	1.43 [1.25,1.64]
	>45	7886	565	7.2 [6.6,7.8]	1.39 [1.19,1.63]
Sex	Male	26594	2427	9.1 [8.8,9.5]	1.75 [1.63,1.88]
	Female	27287	1201	4.4 [4.2,4.7]	ref
BMI (kg/m^2)	<18.5	16801	1901	11.3 [10.8,11.8]	1.97 [1.83,2.11]
	18.5-22.9	23980	1206	5.0 [4.8,5.3]	ref
	23-27.5	8878	319	3.6 [3.2,4]	0.74 [0.65,0.84]
	>27.5	4223	202	4.8 [4.2,5.5]	0.93 [0.80,1.08]
RBG (mg/dl)	<140 (euglycemic)	50981	3361	6.6 [6.4,6.8]	ref
	≥140 (hyperglycemia)	2900	267	9.2 [8.2,10.4]	1.22 [1.08,1.39]
Alcohol drinking	Never	38956	2102	5.4 [5.2,5.6]	ref
	Habitual (daily)	3008	449	14.9 [13.6,16.4]	2.1 [1.90,2.33]
	Social (weekly)	11079	1012	9.1 [8.6,9.7]	1.4 [1.30,1.51]
	Not recorded	837	65	7.8 [6.1,9.9]	1.06 [0.83,1.36]
CD4 cell count (cells/mm^3)	>350	12181	381	3.1 [2.8,3.5]	ref
	200-349	14844	601	4.0 [3.7,4.4]	1.44 [1.27,1.64]
	<200	26792	2611	9.7 [9.4,10.1]	3.18 [2.86,3.54]
	unknown	64	35	54.4 [39,75.7]	3.39 [2.39,4.79]
WHO clinical staging	Stage 1 or 2	33244.89	852.0	2.6 [2.4,2.7]	ref
	Stage 3 or 4	20635.934	2776.0	13.5 [13.0,14.0]	4.65 [4.30,5.02]
Anemia	No	22624	628	2.8 [2.6,3.0]	ref
	Mild or Moderate	28819	2444	8.5 [8.2,8.8]	2.85 [2.61,3.12]
	Severe	2009	515	25.6 [23.5,27.9]	6.12 [5.44,6.87]

	Not recorded	428	41	9.6 [7.0,13.0]	2.09 [1.52,2.87]
Hepatitis B surface antigen	Negative	47062	3040	6.5 [6.2,6.7]	ref
	Positive	4311	304	7.1 [6.3,7.9]	1.06 [0.94,1.19]
	Not recorded	2508	284	11.3 [10.1,12.7]	0.99 [0.87,1.12]
Hepatitis C antibody	Negative	46665	2953	6.3 [6.1,6.6]	ref
	Positive	4684	389	8.3 [7.5,9.2]	1.06 [0.95,1.18]
	Not recorded	2532	286	11.3 [10.1,12.7]	0.99 [0.88,1.12]
Prior exposure to ART	No	50376	3554	7.1 [6.8,7.3]	ref
	Yes	3505	74	2.1 [1.7,2.7]	0.39 [0.31,0.49]
On ART during follow-up	No	981	199	20.3 [17.7,23.3]	ref
	Yes	52900	3429	6.5 [6.3,6.7]	1.14 [0.99,1.32]

IR: incidence rate, HR: hazard ratio; BMI: body mass index; RBG: random blood glucose; ART: antiretroviral therapy

*All characteristics were measured at enrollment to HIV care except the last variable, whether the patient was on ART during follow-up or not.

Table 2. Association between body mass index and random blood glucose level with incident TB among people living with HIV enrolled Integrated HIV Care Program, 2011-2017, Myanmar

		IR [95% CI]	IR difference [95%CI]	HR [95% CI]	aHR* [95%CI]
BMI (kg/m^2)					
Continuous predictor (increase in one unit of BMI)		-	-	0.92 [0.90, 0.93]	0.97 [0.96, 0.98]
Categorical model (Dichotomous)	<18.5 (Low)	11.3 [10.8, 11.8]	6.6 [6.1, 7.2]	2.11 [1.97, 2.25]	1.41 [1.32, 1.51]
	≥18.5 (Normal/high)	4.7 [4.4, 4.8]	Ref	Ref	Ref
Categorical model (4 level)	<18.5 (Low)	11.3 [10.8, 11.8]	6.3 [5.7, 6.9]	1.97 [1.83, 2.11]	1.44 [1.33, 1.55]
	18.5-22.9 (Normal)	5.0 [4.8, 5.3]	Ref	Ref	Ref
	23-27.5 (Overweight)	3.6 [3.2, 4.0]	-1.4 [-1.9, -0.9]	0.74 [0.65, 0.84]	0.95 [0.84, 1.08]
	>27.5 (Obese)	4.8 [4.2, 5.5]	-0.3 [-0.9, 0.05]	0.93 [0.80, 1.08]	1.36 [1.17, 1.59]
Restricted cubic spline	16.0	-	-	2.71 [2.48, 2.97]	1.61 [1.46, 1.77]
	18.5	-	-	1.89 [1.73, 2.05]	1.30 [1.19, 1.42]
	23.0	-	-	Ref	Ref
	27.5	-	-	0.95 [0.91, 1.00]	1.09 [1.04, 1.14]
Random Blood Glucose (mg/dl)					
Continuous predictor (increase in one unit)		-	-	1.00 [1.00, 1.00]	1.00 [1.00, 1.00]
Categorical model (Dichotomous)	Euglycemia (<140)	6.6 [6.4,6.8]	Ref	Ref	Ref
	Hyperglycemia (≥140)	9.2 [8.2,10.4]	2.6 [1.5, 3.7]	1.22 [1.08, 1.39]	1.17 [1.03, 1.32]
Categorical model (4 level)	<110	6.3 [6.1,6.5]	Ref	Ref	Ref
	110-139	8.3 [7.7,9]	2.0 [1.3, 2.7]	1.21 [1.10, 1.32]	1.17 [1.07, 1.28]
	141-199	9.4 [8.3,10.7]	3.1 [1.8, 4.3]	1.26 [1.11, 1.45]	1.19 [1.05, 1.37]
	>199	8.1 [5.9,11.4]	1.8 [-0.9, 4.5]	1.24 [0.89, 1.73]	1.23 [0.89, 1.72]
Restricted Cubic Spline	110	-	-	Ref	Ref
	140	-	-	1.06 [1.02,1.11]	1.05 [1.00,1.10]
	199	-	-	1.09 [0.92, 1.29]	1.10 [0.93, 1.30]
	240	-	-	1.11 [0.86. 1.43]	1.14 [0.88, 1.47]

IR: incidence rate per 100 person-years, HR: hazard ratio, aHR: adjusted HR, RBG: random blood glucose level, BMI: body mass index, Ref: reference group

*adjusted for age, sex, CD4 counts, anemia and alcohol drinking status at registration and ART status during follow-up

Table 3. Risk incident TB by joint exposure to hyperglycemia and low BMI among people living with HIV enrolled Integrated HIV Care Program, 2011-2017, Myanmar

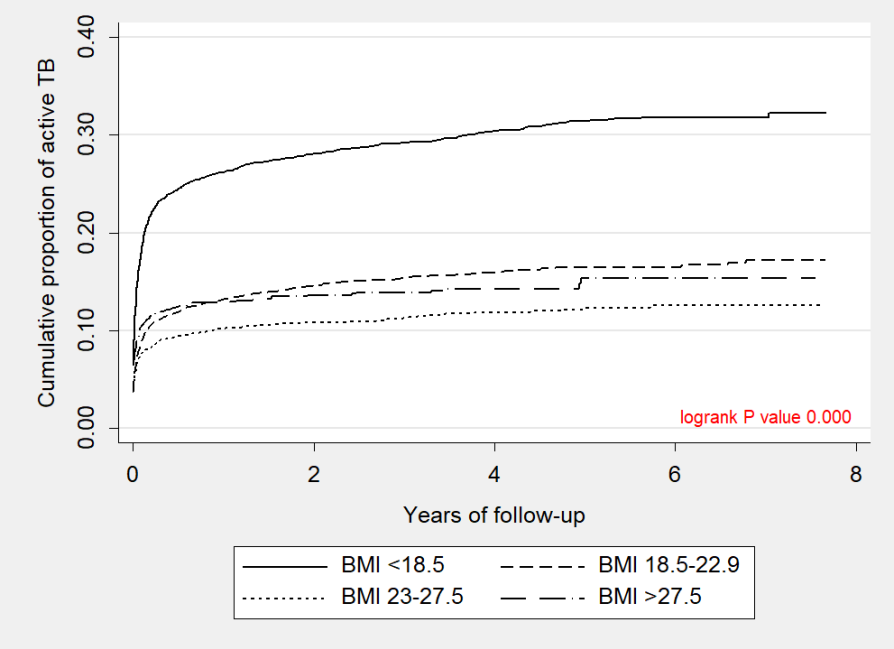
RBG (mg/dl)	BMI (kg/m^2)	Total n	Incident TB n	IR [95% CI]	IR difference	HR [95% CI]	aHR* [95% CI]
Euglycemia (<140)	≥18.5	12,387	1613	4.6 [4.4,4.9]	Ref	Ref	Ref
	<18.5 (Low)	7,154	1748	10.9 [10.4, 11.4]	**6.3 [5.7, 6.8]**	**2.06 [1.92, 2.20]**	**1.39 [1.30, 1.49]**
Hyperglycemia (≥140)	≥18.5	868	114	5.2 [4.4, 6.3]	0.6 [-0.4, 1.6]	1.04 [0.86, 1.25]	1.03 [0.85,1.24]
	<18.5 (Low)	456	153	21.0 [18, 24.7]	**16.4 [13.1, 19.8]**	**3.09 [2.62, 3.64]**	**1.84 [1.55, 2.18]**

RBG: random blood glucose level, BMI: body mass index, IR: incidence rate per 100 person-years, HR: hazard ratio, aHR: adjusted HR, Ref: reference group

*adjusted for age, sex, CD4 counts, anemia and alcohol drinking status at registration and ART status during follow-up

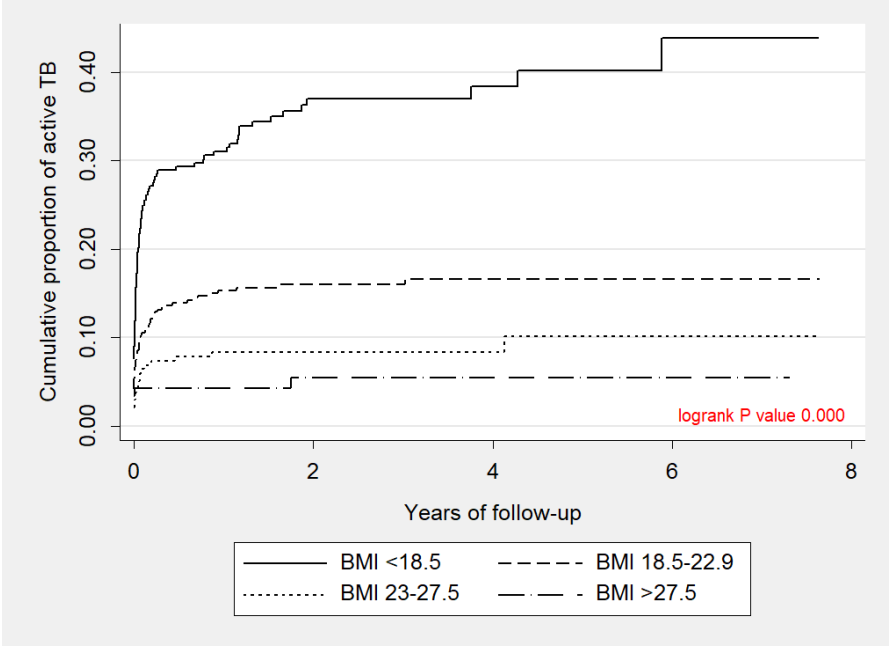
Figure 1. Estimated cumulative hazard of active TB during follow-up stratified by body mass index among people living with HIV enrolled in Integrated HIV Care Program, 2011-2017, Myanmar

(a) Patients with euglycemia (RBG <140 mg/dl)



BMI: body mass index (kg/m^2)

(b) Patients with hyperglycemia (RBG ≥140 mg/dl)



BMI: body mass index (kg/m^2)

Supplemental Table 1. Enrollment characteristics of people living with HIV included and excluded in the study

	Total		Included		Excluded	
	No.	Row %	No.	Row %	No.	Row %
	41,179		20,865	50.7	20,314	49.3
Age (year)						
<25	3,132	7.6	1,690	8.1	1,442	7.1
25-45	31,252	75.9	15,873	76.1	15,379	75.7
>45	6,795	16.5	3,302	15.8	3,493	17.2
Sex						
Male	23,896	58.0	11,538	55.3	12,358	60.8
Female	17,283	42.0	9,327	44.7	7,956	39.2
Alcohol drinking						
Never	26,183	63.6	13,856	66.4	12,327	60.7
Habitual (daily)	3,709	9.0	1,582	7.6	2,127	10.5
Social (weekly)	9,568	23.2	5,001	24.0	4,567	22.5
Not recorded	1,719	4.2	426	2.0	1,293	6.4
CD4 cell count (cells/mm^3)						
>350	7,535	18.3	4,627	22.2	2,908	14.3
200-349	8,302	20.2	5,083	24.4	3,219	15.8
<200	20,588	50.0	10,977	52.6	9,611	47.3
Not recorded	4,754	11.5	178	0.9	4,576	22.5
WHO clinical staging						
stage 1 or 2	17,590	42.7	11,419	54.7	6,171	30.4
stage 3 or 4	22,672	55.1	9,446	45.3	13,226	65.1
Not recorded	917	2.2	0	0.0	917	4.5
Previous ART before enrolled						
No	24,182	87.4	12,515	89.4	11,667	85.4
Yes	3,483	12.6	1,481	10.6	2,002	14.6
Anemia						
No	11,812	28.7	7,722	37.0	4,090	20.1
Mild or Moderate	21,084	51.2	11,511	55.2	9,573	47.1
Severe	3,200	7.8	1,348	6.5	1,852	9.1
Not recorded	5,083	12.3	284	1.4	4,799	23.6
Hepatitis B surface antigen						
Negative	31,889	77.4	17,380	83.3	14,509	71.4
Positive	2,995	7.3	1,672	8.0	1,323	6.5
Not recorded	6,295	15.3	1,813	8.7	4,482	22.1
Hepatitis C antibody						
Negative	31,281	76.0	16,898	81.0	14,383	70.8
Positive	3,542	8.6	2,142	10.3	1,400	6.9
Not recorded	6,356	15.4	1,825	8.7	4,531	22.3

RBG, mg/dl						
Euglycemia (<140)	27,820	67.6	19,541	93.7	8,279	40.8
Hyperglycemia (≥140)	1,944	4.7	1,324	6.3	620	3.1
Not recorded	11,415	27.7	0	0.0	11,415	56.2
BMI (kg/m^2)						
<18.5	13,135	31.9	7,610	36.5	5,525	27.2
18.5-22.9	13,251	32.2	8,669	41.5	4,582	22.6
23-27.5	4,526	11.0	3,028	14.5	1,498	7.4
>27.5	2,366	5.7	1,558	7.5	808	4.0
Not recorded	7,901	19.2	0	0.0	7,901	38.9

Supplemental Table 2. Baseline characteristics of people living with HIV enrolled Integrated HIV Care Program, 2011-2017, Myanmar stratified by body mass index

			BMI category							
		Total	Underweight <18.5 kg/m^2		Normal 18.5-22.9 kg/m^2		Overweight 23-27.5 kg/m^2		Obese >27.5 kg/m^2	
		No.	No.	Row %	No.	Row %	No.	Row %	No.	Row %
	Total	20,865	7,610	36.5	8,669	41.5	3,028	14.5	1,558	7.5
Age (year)	<25	1,690	626	37	728	43.1	212	12.5	124	7.3
	25-45	15,873	5,698	35.9	6,699	42.2	2,331	14.7	1,145	7.2
	>45	3,302	1,286	38.9	1,242	37.6	485	14.7	289	8.8
Sex	Male	11,538	4,526	39.2	5,116	44.3	1,441	12.5	455	3.9
	Female	9,327	3,084	33.1	3,553	38.1	1,587	17	1,103	11.8
Alcohol drinking	Never	13,856	5,013	36.2	5,488	39.6	2,103	15.2	1,252	9
	Habitual (daily)	1,582	708	44.8	654	41.3	169	10.7	51	3.2
	Social (weekly)	5,001	1,743	34.9	2,339	46.8	694	13.9	225	4.5
	Not recorded	426	146	34.3	188	44.1	62	14.6	30	7
CD4 cell count (cells/mm^3)	>350	4,627	989	21.4	2,086	45.1	956	20.7	596	12.9
	200-349	5,083	1,326	26.1	2,384	46.9	899	17.7	474	9.3
	<200	10,977	5,200	47.4	4,141	37.7	1,157	10.5	479	4.4
	Not recorded	178	95	53.4	58	32.6	16	9	9	5.1
WHO clinical staging	stage 1 or 2	11,419	2,840	24.9	5,349	46.8	2,148	18.8	1,082	9.5
	stage 3 or 4	9,446	4,770	50.5	3,320	35.1	880	9.3	476	5
Anemia	No	7,722	1,671	21.6	3,687	47.7	1,603	20.8	761	9.9
	Mild or Moderate	11,511	4,978	43.2	4,497	39.1	1,297	11.3	739	6.4
	Severe	1,348	845	62.7	371	27.5	87	6.5	45	3.3
	Not recorded	284	116	40.8	114	40.1	41	14.4	13	4.6
Hepatitis B surface antigen	Negative	17,380	6,157	35.4	7,224	41.6	2,625	15.1	1,374	7.9
	Positive	1,672	592	35.4	743	44.4	228	13.6	109	6.5

	Not recorded	1,813	861	47.5	702	38.7	175	9.7	75	4.1
Hepatitis C antibody	Negative	16,898	6,124	36.2	6,851	40.5	2,519	14.9	1,404	8.3
	Positive	2,142	619	28.9	1,112	51.9	333	15.5	78	3.6
	Not recorded	1,825	867	47.5	706	38.7	176	9.6	76	4.2
RBG, mg/dl (Median, IQR)		88.2 (75.6 – 106.2)	88.2 (75.0 – 106.2)		88.2 (75.6 – 106.2)		88.9 (75.6 – 108.0)		87 (75.0 – 103.0)	
RBG, mg/dl (2 categories)	Euglycemia (<140)	19,541	7,154	36.6	8,161	41.8	2,787	14.3	1,439	7.4
	Hyperglycemia (≥140)	1,324	456	34.4	508	38.4	241	18.2	119	9
RBG, mg/dl (4 categories)	<110	16,493	6,043	36.6	6,868	41.6	2,335	14.2	1,247	7.6
	110-140	3,057	1,113	36.4	1,295	42.4	453	14.8	196	6.4
	141-199	1,141	400	35.1	450	39.4	202	17.7	89	7.8
	>199	174	54	31	56	32.2	38	21.8	26	14.9
Prior exposure to ART	No	19,891	7,355	37	8,215	41.3	2,831	14.2	1,490	7.5
	Yes	974	255	26.2	454	46.6	197	20.2	68	7

BMI: body mass index; ART: antiretroviral therapy; RBG: random blood glucose

Chi-square test for all categorical variables and Kruskal-Wallis rank sum test for all continuous variables resulted *P* value <0.05

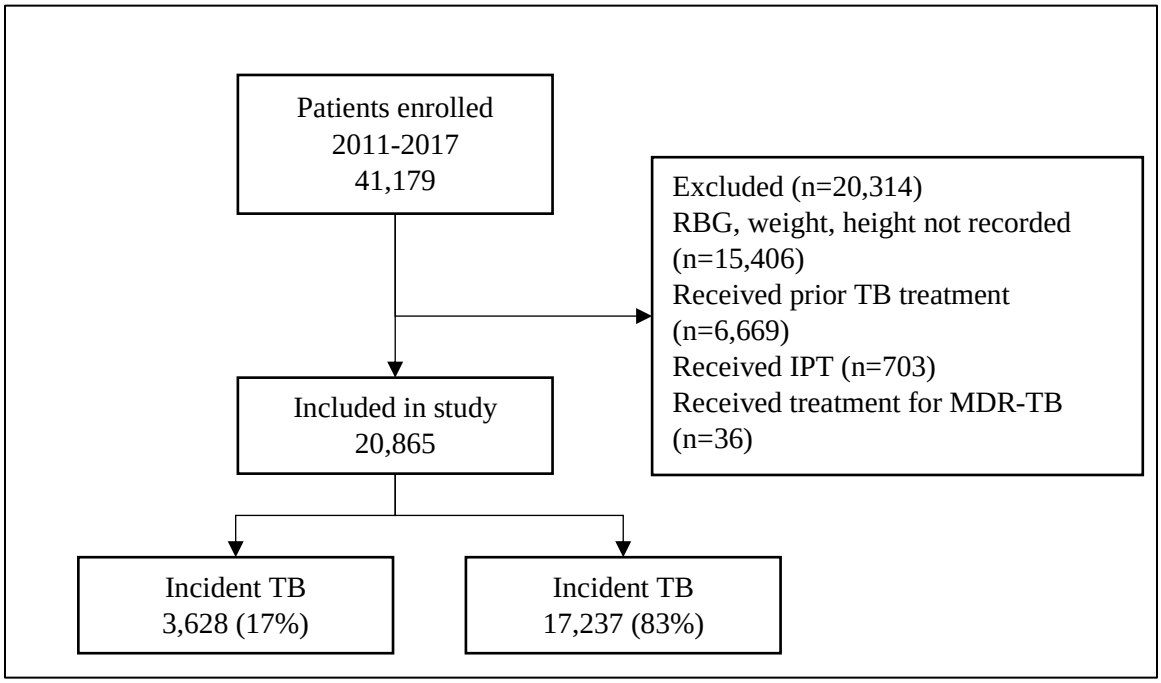
Supplemental Table 2. Interaction between low body mass index and hyperglycemia with the risk of active TB among people living with HIV enrolled Integrated HIV Care Program, 2011-2017, Myanmar <u>after excluding patients with TB disease diagnosed with three months of enrollment</u> (n=17,967)

Random blood glucose (mg/dl)	BMI (kg/m^2)	Total n	Incident TB n	IR [95% CI]	IR difference	HR [95% CI]	aHR [95% CI]
Normoglycemia (RBG ≤140)	≥18.5	11,156	382	1.1 [1.0, 1.2]	Ref	Ref	Ref
	<18.5 (Low)	5,711	305	1.9 [1.7, 2.1]	0.8 [0.5, 1.0]	**1.78 [1.52,.2.05]**	**1.35 [1.16, 1.58]**
Hyperglycemia (RBG >140)	≥18.5	771	17	0.8 [0.5, 1.3]	-0.3 [-0.7, 0.1]	0.69 [0.43, 1.14]	0.72 [0.44, 1.17]
	<18.5 (Low)	329	26	3.6 [2.5, 5.28]	2.5 [1.1, 4.9]	**3.11 [2.09, 4.62]**	**2.23 [1.49, 3.33]**

RBG: random blood glucose level, BMI: body mass index, IR: incidence rate per 100 person-years, HR: hazard ratio, aHR: adjusted HR, Ref: reference group

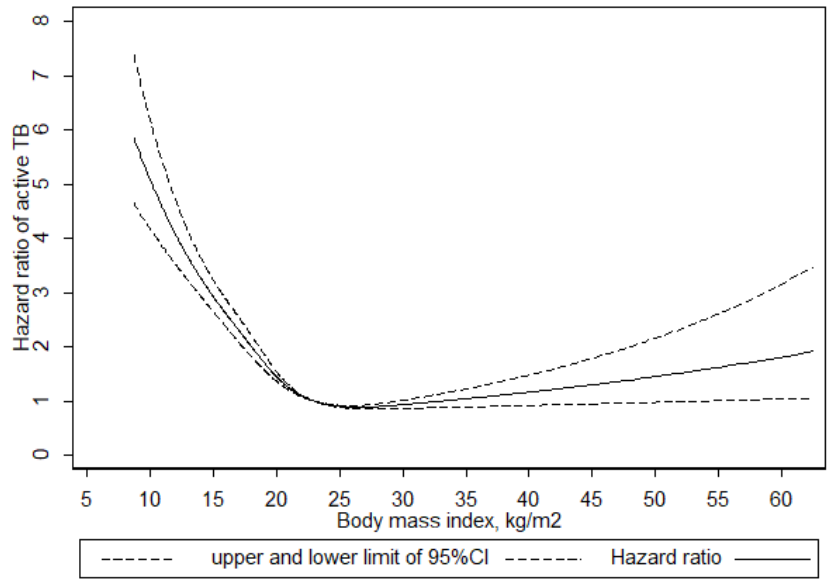
*adjusted for age, sex, CD4 counts, anemia and alcohol drinking status at registration and ART status during follow-up

Supplemental Figure 1. Flow diagram of the people living with HIV enrolled under Integrated HIV Care program in Myanmar 2011-2017



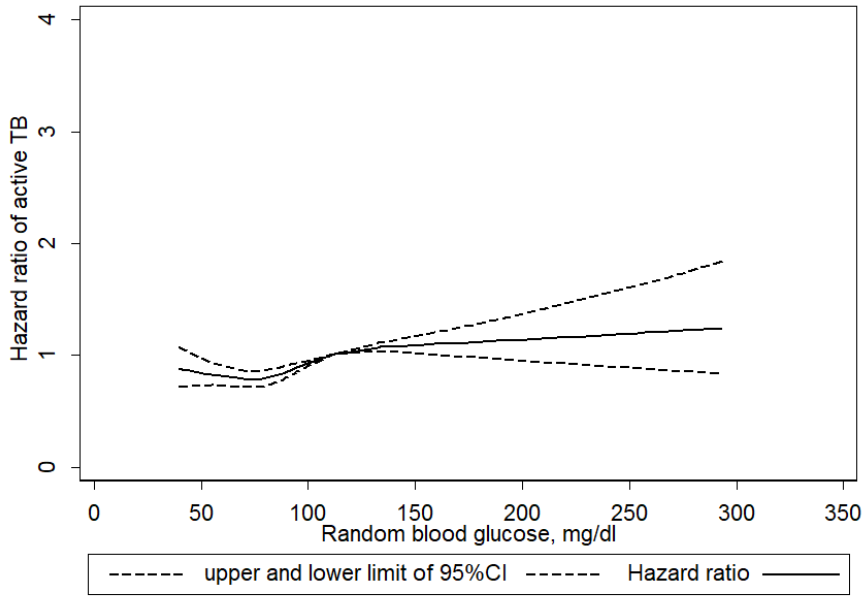
RBG: random blood glucose, IPT: isoniazid preventive therapy, TB: tuberculosis, MDR-TB: multidrug resistant TB

Supplemental Figure 2.a. Estimated hazard ratio of active TB across body mass index among people living with HIV enrolled Integrated HIV Care Program, 2011-2017, Myanmar using restricted cubic spline regression*



* using 4 knots at equally spaced percentiles with a reference point at 18.5 kg/m2

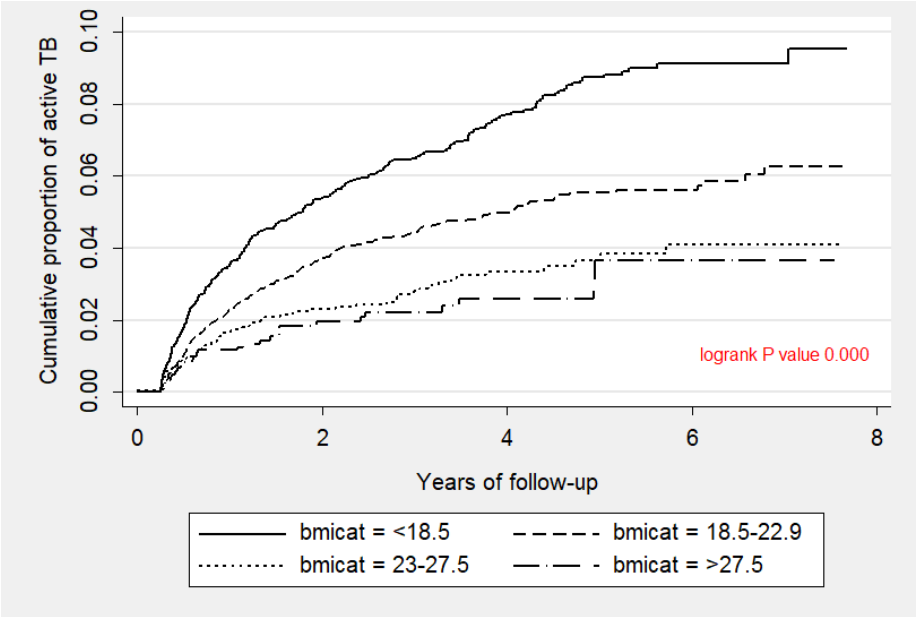
Supplemental Figure 2.b. Estimated hazard ratio of active TB across random blood glucose level among people living with HIV enrolled Integrated HIV Care Program, 2011-2017, Myanmar using restricted cubic spline regression*



* using 4 knots at equally spaced percentiles with a reference point at 110mg/dl

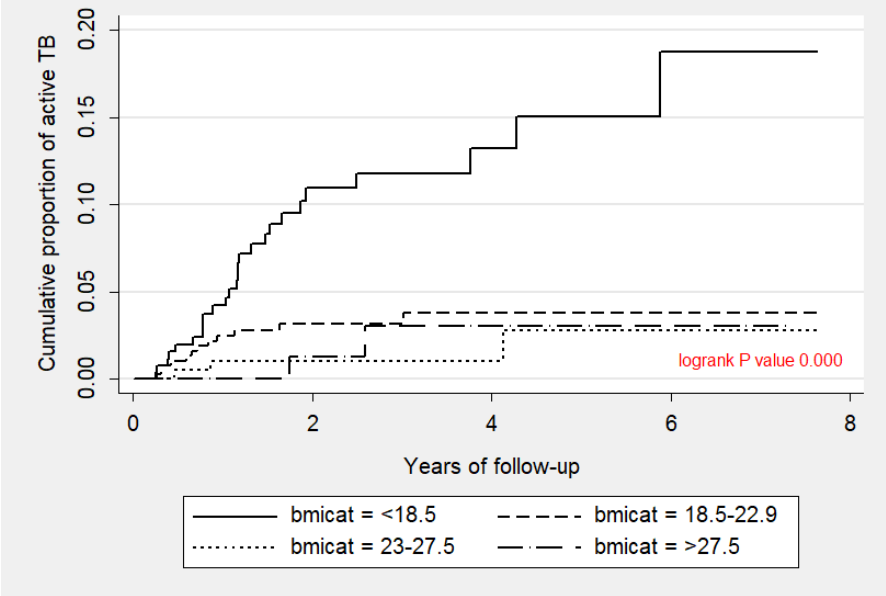
Supplemental Figure 3. Estimated cumulative hazard of active TB during follow-up stratified by body mass index among people living with HIV enrolled in Integrated HIV Care Program, 2011-2017, Myanmar <u>after excluding patients with TB disease diagnosed with three months of enrollment</u> (n=17,967)

(a) Patients with euglycemia (RBG <140 mg/dl)



bmicat: body mass index category (kg/m^2)

(b) **Patients with hyperglycemia**



bmicat: body mass index category (kg/m^2)

Chapter 3: Paper 2- Association between prevalent TB with HIV clinical outcomes and role of blood glucose level as mediator in association between prevalent TB and all-cause mortality (In Progress)

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ABSTRACT

Background

Active TB is a known risk factor for all-cause mortality and unfavorable immunological and virological responses in people living with HIV (PLHIV). Hyperglycemia is also associated with risk of active TB disease and all-cause mortality. Among PLHIV, we estimated i) the association between active TB with one-year all-cause mortality, and CD4 recovery and ii) whether glycemic level mediates the association between active TB and all-cause mortality.

Methods

Antiretroviral therapy (ART) naïve PLHIV aged ≥15 years entering care (enrollment) between 2011 and 2018 in an outpatient HIV clinic, Taunggyi city, Myanmar were eligible. Active TB was defined if PLHIV was on TB treatment at enrollment or started TB treatment within 90 days of enrollment. Glycemic level was determined by random blood glucose (RBG) measured by glucometer using capillary blood at enrollment to HIV care. We used a log binomial models to estimate the association between active TB on mortality and a general linear mixed model to estimate the association between active TB with change in CD4 count. We conducted a mediation analysis using a product method to estimate direct, indirect and total effects of active TB on mortality through glycemic levels.

Results

Of 2,035 PLHIV entered to care, 1,871 were included in the analysis. Among them, 687 (37%) had CD4 count <100 cell/mm^3 and 394 (21%) had active TB. The median RBG level was 86 mg/dl (interquartile range: 74, 99). During one-year follow-up, 21% of the PLHIV in the cohort died and

the mortality was significantly higher in PLHIV with active TB [adjusted relative risk:1.75, 95% CI:1.38, 2.21]. The mean log CD4 count during the follow-up was significantly lower in PLHIV with active TB compared to those without active TB [β_{TB} = -0.61, 95% CI: -0.71, -0.51, $\beta_{TB*follow\text{-}up\ month}$= 0.04, 95% CI: 0.03, 0.05], however, there was an upward trajectory of CD4 count after ART in both groups. We did not observe glycemic status to be a key mediator in the relationship between active TB and all-cause mortality.

Conclusion

One in five PLHIV had active TB in this cohort and the risk of mortality was higher in PLHIV with active TB compared to those without active TB. Scaling up of TB preventive intervention in this PLHIV cohort should be considered to reduce mortality among PLHIV.

INTRODUCTION

Globally, one million out of 38 million people living with HIV (PLHIV) died in 2018 [3]. Tuberculosis (TB) is the principal comorbidity and leading cause of death accounting for 251,000 HIV-related deaths(range: 223,000-281,000) [146]. Due to host-pathogen interactions, the mortality risk of PLHIV with TB is two to four-fold higher compared to those who have HIV infection alone [26,33]. One of the mechanisms of increased mortality due to TB is that HIV depletes CD4 cells which are essential for autophagic clearance of TB bacteria leading to an increase in bacterial load and severe TB disease in PLHIV [19,27]. In addition, during host immune response to active TB, there is an increased T cells accumulation, rapid HIV replication in T cells and direct T cells to cells HIV spread which are associated with higher HIV viral load and rapid HIV disease progression [174]. Studies from African countries showed that PLHIV with TB treatment at ART initiation had lower CD4 cell counts at baseline but greater increases in CD4+T cell during follow-up [175–177]. However, there is a dearth of knowledge from high HIV/TB burden countries in Asia on the impact of active TB on CD4 T+ cells after the start of antiretroviral therapy (ART) [178].

Most HIV/TB coinfection and associated mortality occurred in resource limited settings in early ART era before 2010. During that time, ART availability was limited and PLHIV were initiated on ART in late disease stage which increased the risk of TB related mortality due to depleted CD4 cells [28]. With increased ART coverage during the last decade in many high HIV/TB burden countries, it is important to assess other factors that might contribute to increased risk of mortality associated with TB disease.

Hyperglycemia, the main clinical feature of type 2 diabetes mellitus, is an emerging comorbidity in PLHIV, and occurs as a result of adverse events of commonly used ART and/or the increased risk of metabolic disease amongst an aging PLHIV population [58–61,64]. Previous studies have suggested that hyperglycemia in PLHIV is associated with an increased risk of death and adverse outcomes due to worsening diabetes, HIV or ART related complications [68–70,145].

On the other hand, emerging evidence suggests that TB disease increases the risk of stress hyperglycemia, a state of transient hyperglycemia induced by the acute illness of TB disease [103,104]. Although there is no evidence yet in the context of HIV, stress hyperglycemia in other critical illnesses is associated with adverse clinical outcomes and increased mortality [179–182]. Hence, it is plausible that the increased risk of TB-related mortality in PLHIV may be mediated by hyperglycemia. Among PLHIV, improved understanding of the role of hyperglycemia in TB related mortality may inform therapeutic efforts to optimize glycemic control and thereby reduce mortality in HIV/TB patients. There are reviews and guidelines currently used to address the control of the hyperglycemia in TB patients [183,184]. More evidence, however, is needed to better formulate clinical guidelines for the management of TB and hyperglycemia in PLHIV to reduce adverse TB and HIV outcomes. In this study, we estimated the association between active TB with all-cause mortality, change in CD4 cells and virological failure after one year on ART. We also assessed whether blood glucose level mediates the association between active TB and all-cause mortality among PLHIV.

METHODS

Study population

Adult PLHIV >15 years old enrolled between 2011 and 2018 in an outpatient HIV clinic in Taunggyi city, Myanmar, who were antiretroviral therapy (ART) naïve, had TB treatment information and random blood glucose (RBG) measurements at enrollment were eligible. Pregnant women, PLHIV without RBG measurements, drug resistant TB cases and those taking isoniazid preventive therapy were excluded from the study.

Study Setting

Myanmar is one of the 30 high dual HIV/TB burden countries in the world. The study site for this study was a HIV clinic operated under the Integrated HIV Care Program jointly operated by the National HIV/AIDS program and the International Union Against Tuberculosis and Lung Disease. Standard of care for PLHIV entered the HIV care included RBG, CD4, weight and height measurements, TB disease screening, treatment and prophylaxis for opportunistic infections according to WHO and National HIV treatment guidelines [185,186]. TB disease screening was also done during monthly or quarterly follow-up visits. Active TB diagnosis is based on TB symptoms, acid-fast bacilli (AFB) sputum smears, sputum specimens for Xpert MTB/RIF assays and/or chest X-ray. Clinical details were recorded in individual medical record files by medical officers at each patient visit.

Measures and data sources

The primary exposure of interest was prevalent TB disease. PLHIV who were on TB treatment at study enrollment or started TB treatment within 90 days of enrollment were defined

as having prevalent TB disease. PLHIV without a record of TB treatment were classified as not having prevalent TB disease. All forms of TB disease (bacteriologically confirmed, radiologically diagnosed, pulmonary or extra-pulmonary TB disease) were included.

The primary outcome variable was all-cause mortality during one year of follow-up. All-cause mortality was determined using patient medical records. The secondary outcomes included CD4 cell count change and virological failure. In this setting, CD4 cells were measured at enrollment or at the time of starting ART and every 3 to 6 months thereafter using automated flow cytometry (CyFlow® Counter 2, Partec GmbH, Germany) in the public health laboratory. The CD4 cell count was determined using all CD4 measurements from baseline to 15 months of ART as some of the patients received their 12^{th} months of blood investigation a few months later.

Routine viral load testing was performed at 6 or 12 months after the start of ART to monitor virological suppression (this has been the practice since 2017). Viral load testing was carried out using real time PCR (RT-PCR) (GENERIC HIV Viral Load, Biocentric, Bandol, France) which has a lower limit of detection of 250 copies/ml. For the virological failure outcome at one year, we included any viral load result performed between 9 and 15 months after the start of ART. PLHIV with two viral load measurements >1000 copies/ml were considered to have a virological failure.

The mediator variable of interest was the continuous measure of RBG level measured by glucometer using capillary blood at enrollment to HIV care. Other covariates included age, sex, body mass index (BMI), hepatitis B and C status and ART status at enrollment. Patients were considered hepatitis B positive if they had positive HBs antigen test and hepatitis C positive if they had positive HCV antibodies. BMI was calculated from a patient's weight and height (weight in kg / (height in metre)^2) measured at enrollment.

All data were extracted from patients' electronic medical records, which were digitized from a hard copy of the patients' medical record.

Ethics

The study was approved by Institutional Review Board at Georgia State University, the Union Ethics Advisory Group (Paris, France) and Ethics Review Committee at the Department of Medical Research, Ministry of Health and Sports, Myanmar. A waiver of informed consent was granted by ethics review bodies, as the study collected and analyzed de-identified routine recording and reporting data.

Statistical analysis

The analytic goals were to 1) estimate the association of active TB on all-cause mortality, the change in CD4 count, and HIV viral load and 2) determine the mediating role of RBG in the relationship between active TB and all-cause mortality. Patients' characteristics were compared between those with and without active TB using the chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous measures. We used log binomial models to estimate risk ratios and 95% confidence intervals for the relationship between active TB on one-year all-cause mortality. A general linear mixed model with random intercept was used to estimate the association of active TB with CD4 count change during one year of ART. All final regression models were adjusted for potential confounders identified by unadjusted analyses and directed acyclic graph theory [187]. For mediation analysis, we used the product method [188] based on the assumed causal pathway presented in **Figure 1**. We estimated bias-corrected bootstrap confidence intervals (CIs) with 1000 repetition for indirect effect, direct effect, and total effects. The model fit was tested using F-test and R^2 for linear regression, AIC and scaled deviance and

Pearson Chi-square test for log binomial model, and F-test and AIC for general linear mixed model. The level of significance was set at 0.05.

RESULTS

Study population

Of 2,035 PLHIV enrolled at the study site between 2011 and 2018, pregnant women (n=67), PLHIV who had not had RBG measurements (n=89), those who were taking isoniazid preventive therapy (n=8) and initiated TB treatment two months before enrollment were excluded from the study (**Figure 1**). Of 1,871 PLHIV included in the analysis, 1,598 PLHIV initiated on ART and 1,571 had baseline CD4 measurements. At enrollment, the median RBG level of the study cohort was 86 mg/dl [IQR: 74, 99], 691 (37%) patients had BMI <18.5 kg/m^2 and 687 (37%) had CD4 cell counts <100 cell/ mm^3 (**Table 1**).

Overall, the prevalence of active TB was 21%. The median RBG among PLHIV with no TB disease was 87 mg/dl [interquartile range (IQR): 74, 101] and among those with TB disease was 85 mg/dl [IQR:72,95]. The prevalence of active TB was different across patients' sex, age, BMI, CD4 cell count, WHO clinical staging, anemia and ART status at enrollment **(Table 1)**.

Association between prevalent active TB on all-cause mortality, change in CD4 count, and virological response

We compared all-cause mortality among PLHIV with and without active TB. The proportion of PLHIV who died from any cause during one year of follow-up among patients with

active TB was higher than among those without active TB (20% vs 13%) **(Table 2**). The unadjusted risk of all-cause mortality among PLHIV with active TB was 1.55 (95% CI: 1.21, 1.97) times the risk in those without active TB. After controlling for age, sex, duration on ART and glycemic level, the adjusted relative risk was 1.75 (95%CI: 1.38, 2.21) and when CD4 count, BMI and anemia status were included in the adjusted model, the relative risk was 1.01 (95% CI: 0.80, 1.27) **(Table 2**).

The median baseline CD4+T cell count was 135 cell/mm^3 [IQR: 52, 271]. The CD4+T cell results after one year of ART were available in 549 patients and the median was 284 cell/mm^3 [IQR: 189,478]. We fitted a linear mixed model using the log transformation of CD4 +T cell count to estimate the change of CD4 counts during one-year follow-up on ART as a function of active TB and follow-up time. The interaction term between active TB status and time was included in the model. There was an upward trend of changes in CD4 cell counts after ART and the trend was significant irrespective of the patient's active TB status **(Figure 3)**. However, a patient with active TB had a significantly lower mean CD4 cell count compared to those without active TB [β_{TB} = -0.61, 95% CI: -0.71, -0.51, $\beta_{TB*follow\text{-}up\ month}$= 0.04, 95% CI: 0.03, 0.05] (**Supplemental Table 1).**

Among PLHIV initiated on ART, 182 (10%) were tested for viral load between 9 and 15 months after starting ART. Among those tested, 37 (20%) had detectable viral load. A lower proportion of PLHIV with active TB were tested for viral load (8% vs 12%) and a higher proportion had detectable viral load (25% vs 20%) (**Table 3**). As only 50% of PLHIV with detectable viral load were tested for viral load again, we cannot make any meaningful assessment of association between active TB and one-year virological failure.

Mediating effect of blood glucose level on association between active TB and mortality

The adjusted estimated coefficients of the regression models of mediation analyses are presented in **Figure 2**. In model 1, we included age and sex as potential confounders and in model 2, age, sex, CD4 cells and BMI as potential confounders. Active TB was associated with a lower glycemic level. The average RBG level in PLHIV with active TB disease was 0.29 mg/dl lower than in those without active TB after adjusting for age, sex (result from model 1). The direct effect, indirect effect and total effect of active TB on mortality are presented in **Table 4**. From the adjusted model 1, the direct effect or the relative risk of mortality in patients with active TB was 1.546 times compared to those without active TB after controlling for mediator [95% CI: 1.207, 1.991]. However, the indirect effect of active TB on mortality through glycemia was 0.986 [95% CI: 0.962, 0.999]. We did not calculate the proportion mediated as the direct and indirect effect are not in the same direction.

DISCUSSION

The prevalence of TB disease in this PLHIV cohort is very high as one in five PLHIV had TB disease. Overall mortality was high with 14% of the cohort died during one year of follow-up. PLHIV with active TB had 70% higher one-year all-cause mortality compared to those without active TB. Our study showed that CD4 cell count of PLHIV with active TB increased after ART. Despite this, PLHIV with active TB had a lower CD4 cell count than those without active TB after one year on ART. A finding that was contrary to our hypothesis and the current literature was that active TB disease was associated with lower glycemic levels.

Similar to the findings from African studies, we observed an association between active TB and one-year all-cause mortality in this HIV cohort [28–30]. The association was closed to null

after adjusting for CD4 count, BMI and anemia. However, we believed that CD4 count, BMI and anemia are mediators variables between active TB and mortality or they are ancestor or cause of the TB disease in causal pathway [187] which are not needed to adjust as they are not confounders.

The CD4 count of PLHIV with active TB in this cohort increased one year after ART initiation. This finding was similar to the finding from the systematic review that compared the CD4 response in patients with TB and without TB showed that both groups have the similar CD4 response after ART initiation [178]. However, there are some studies from Africa which showed that HIV/TB coinfected patients are less likely to experience CD4 cell recovery after ART [189–191]. The different in the finding may be due to the difference in defining CD4 cell recovery and not accounting for correlation of CD4 cell count within individual in estimating the CD4 cell response in those studies. As there are very few studies from Asia assessing the impact of active TB on immunological responses using longitudinal CD4 count data, our study results can shed light on the effective immune response among PLHIV with active TB who received ART and anti-TB treatment.

In this cohort, higher proportion of patients with active TB had a viral load >1000 copies/ml after one year on ART compared to those without active TB (25% vs 16%) but the differences were not statistically significant. We cannot assess the association between active TB and virological failure because in this cohort because only a small proportion of patients (11%) were tested for viral load at one year of starting ART and 15 out of 31 patients with viral load >1000 copies/ml repeated the viral load testing.

Our mediation analysis suggested that the association between active TB and risk of mortality was mediated through glycemic levels, but the direct and indirect effect are in opposite

direction. As a result, the total effect of active TB on risk of mortality was attenuated when blood glucose level was included in the model (direct effect=0.45 and total effect = 0.43). As the risk of TB associated with hyperglycemia is poorly understood, the effect we observed in this study can be plausible mechanism in HIV population or can be by chance. Hence, more research is needed to study the role of glycemia in TB related mortality using fasting blood glucose or HbA1c to inform the management of hyperglycemia and TB comorbidities in HIV population.

This study was subject to limitations. Glycemic level was measured using measurements of RBG which may not reflect underlying glucose control or dysglycemia (hyperglycemia or hypoglycemia). The misclassification of glucose control may bias our results toward or away from the null. We defined prevalent TB using a TB treatment record. There could have been patients who were diagnosed with TB disease but had yet to start TB treatment. However, as far as we know, all the patients diagnosed with active TB were treated unless they died or were lost to follow up before treatment could be started. Not all patients were viral load tested at 6 or 12 months of the start of ART which limited the ability to assess the association between active TB and virological failure. In the adjusted model, we only adjusted for potential confounders using the baseline patient characteristics and some covariates may have time-varying effects on outcome. In addition, there will be other unmeasured confounders such as smoking and other metabolic profiles that can impact on the association between glycemic level and mortality and bias our estimates. As the study population was from one HIV clinics and about 8% of the patients were excluded from the study, our results may not be generalizable to all PLHIV in Myanmar.

CONCLUSIONS

Despite these limitations, our study showed that PLHIV with active TB expereince higher mortality and lower mean CD4 cell counts during the follow-up compared to those who did not have TB, however, they achieved good immune recovery once on ART, and TB treatment. We did not observe the relationship between active TB and virological failure and the glycemic status as a mediator in the relationship between active TB and all-cause mortality. Future studies using HbA1c or fasting blood glucose should be conducted to understand the role of hyperglycemia in increasing the risk of mortality in HIV/TB coinfected patients.

Table 1. Demographic and clinical characteristics of PLHIV with and without active TB who enrolled in Integrated HIV Care Program Clinic in Taunggyi City, Myanmar, 2011-2018

		Total	No active TB		Active TB	
		n	n	%	n	%
		1871	1479	79	392	21
Age in year	15-24	102	89	87.3	13	12.7
	25-45	1,408	1,097	77.9	311	22.1
	≥46	361	293	81.2	68	18.8
Sex	Female	774	637	82.3	137	17.7
	Male	1,097	842	76.8	255	23.2
Random blood glucose mg/dl*		86 (74, 99)	87 (74, 101)		85 (72,95)	
BMI kg/m^2	<18.5	691	463	67	228	33
	18.5-22.9	688	586	85.2	102	14.8
	23-27.5	221	206	93.2	15	6.8
	>27.5	40	37	92.5	3	7.5
	Unknown	231	187	81	44	19
Alcohol drinking	Never	1,333	1,038	77.9	295	22.1
	Habitual	172	142	82.6	30	17.4
	Social	326	262	80.4	64	19.6
	Unknown	40	37	92.5	3	7.5
CD4 count cell/mm^3		150 (54, 325)	190 (67, 340)		67 (30, 135)	
CD4count category	>350 cell/mm^3	383	363	94.8	20	5.2
	201-350 cell/mm^3	338	302	89.3	36	10.7
	100-200 cell/mm^3	323	252	78	71	22
	<100 cell/mm^3	688	447	65	241	35
	Unknown	139	115	82.7	24	17.3
WHO staging	1 and 2	888	861	97	27	3
	3 and 4	979	614	62.7	365	37.3
	not recorded	4	4	100	0	0
Anemia	No anemia	681	631	92.7	50	7.3
	Mild to Moderate	934	671	71.8	263	28.2
	Severe	142	80	56.3	62	43.7
	Not recorded	114	97	85.1	17	14.9
Hepatitis B[a]	Negative	878	724	82.5	154	17.5
	Positive	61	49	80.3	12	19.7
	Unknown	932	706	75.8	226	24.2
Hepatitis C[b]	Negative	856	704	82.2	152	17.8
	Positive	83	69	83.1	14	16.9
	Unknown	932	706	75.8	226	24.2

PLHIV: people living with HIV, BMI: body mass index

[a] Tested using hepatitis B surface antigen (Alere Determine™)

[b] Tested using HCV antibody test (OraQuick® immunoassay).

Table 2. All-cause mortality among PLHIV during one year of follow-up according to active TB status

			Alive	Died	Model 1	Model 2	Model 3
		Total	n (%)	n (%)	RR [95% CI]	RR [95% CI]	RR [95% CI]
		1,871	1606 (86)	265 (14)			
Active TB	No	1,479	1291 (87)	188 (13)	Ref	Ref	Ref
	Yes	392	315 (80)	77 (20)	**1.55 [1.21,1.97]**	**1.75 [1.38, 2.21]**	1.01 [0.80,1.27]

RR: risk ratio, PLHIV: people living with HIV, Ref: reference group, Bold indicates 95% confidence interval estimate did not include null value
Model 1: crude RR
Model 2: adjusted for age, sex, duration on ART and blood glucose level
Model 3: adjusted for age, sex, CD4, body mass index, anemia status, duration on ART and blood glucose level

Table 3. HIV viral load testing results after one year of ART among PLHIV with or without active TB enrolled to HIV care between 2011 and 2018 in outpatient HIV clinic in Taunggyi city, Myanmar (n=1598)

	Without active TB n (%)	With active TB n (%)
Total patients initiated on ART	1256	342
Viral load tested at one-year of ART	154 (12%)	28 (8%)
Viral load detectable	30 (20%)	7 (25%)
Viral load >1000 copies/ml	24 (16%)	7 (25%)
Viral load testing repeated	11 (46%)	4 (57%)
Virological failure	6 (55%)	1 (25%)

PLHIV: people living with HIV

Table 4. Estimated direct effect of active TB on all-cause mortality, indirect effect of active TB on mortality through glycemic level and total effect of active TB on all-cause mortality among PLHIV enrolled to HIV care between 2011 and 2018 in outpatient HIV clinic in Taunggyi city, Myanmar

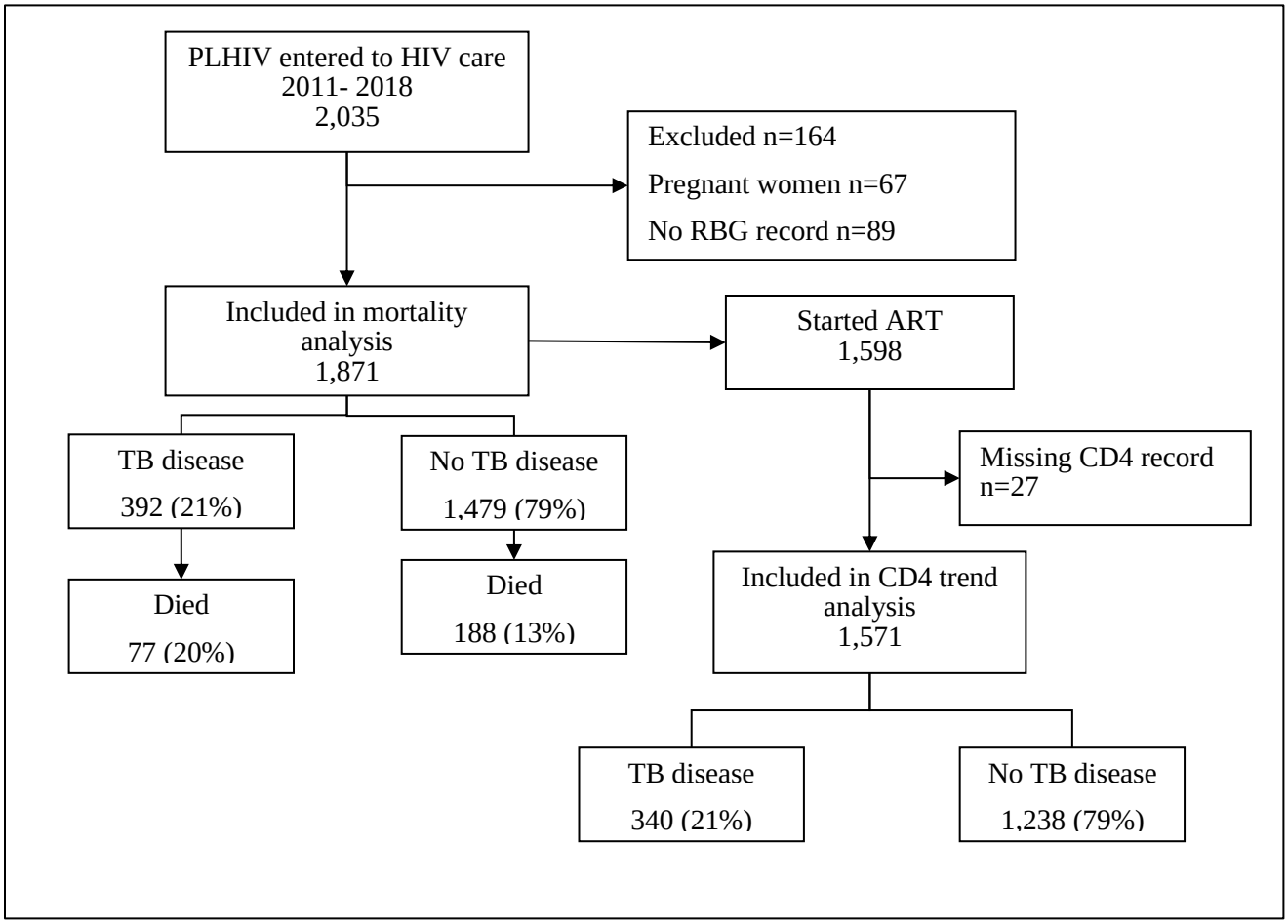
	Unadjusted		Adjusted Model 1		Adjusted Model 2	
	Coefficient	RR [95% CI]	Coefficient	RR [95% CI]	Coefficient	RR [95% CI]
Controlled direct effect	**.455**	**1.576 [1.230, 2.015]**	**.436**	**1.546 [1.207, 1.991]**	0.046	1.047 [0.815,1.351]
Natural indirect effect	**-.017**	**0.983 [0.958,0.998]**	**-.014**	**0.986 [0.962, 0.999]**	-0.004	0.996 [0.975,1.003]
Total effect	**.438**	**1.550 [1.215,1.985]**	**.422**	**1.524 [1.184, 1.956]**	0.042	1.043 [0.809, 1.341]

Model 1: Adjusted for age, sex

Model 2: Adjusted for age, sex, CD4 cell count and body mass index

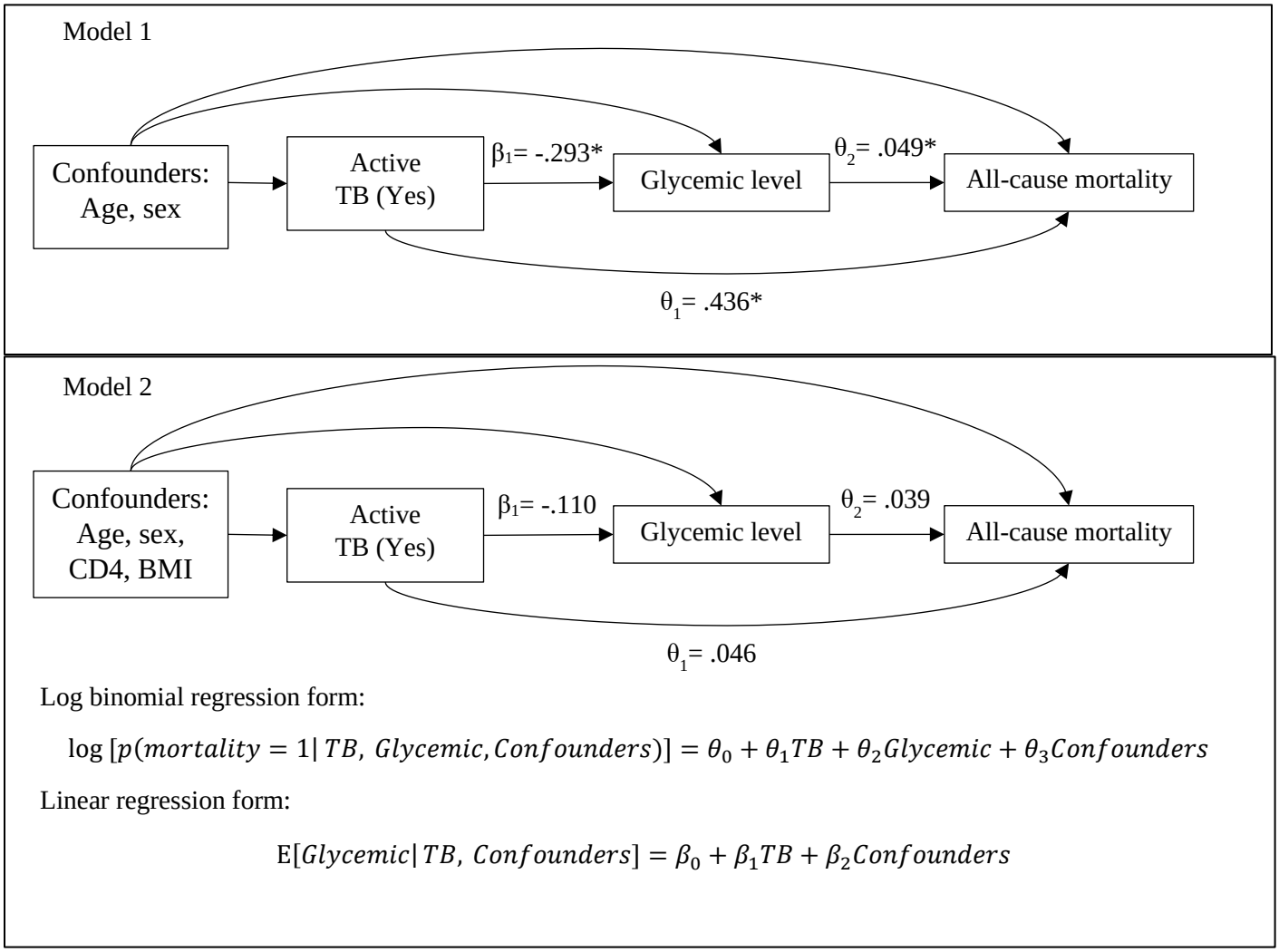
Bold indicates 95% confidence interval estimate did not include null value

Figure 1. Flow diagram of the people living with HIV enrolled under Integrated HIV Care program in Myanmar 2011-2018



TB: tuberculosis, PLHIV: people living with HIV

Figure 2. Directed acyclic graph (DAG) depicting the assumed causal structure for all-cause mortality among people living with HIV due to active TB.



Log binomial regression form:

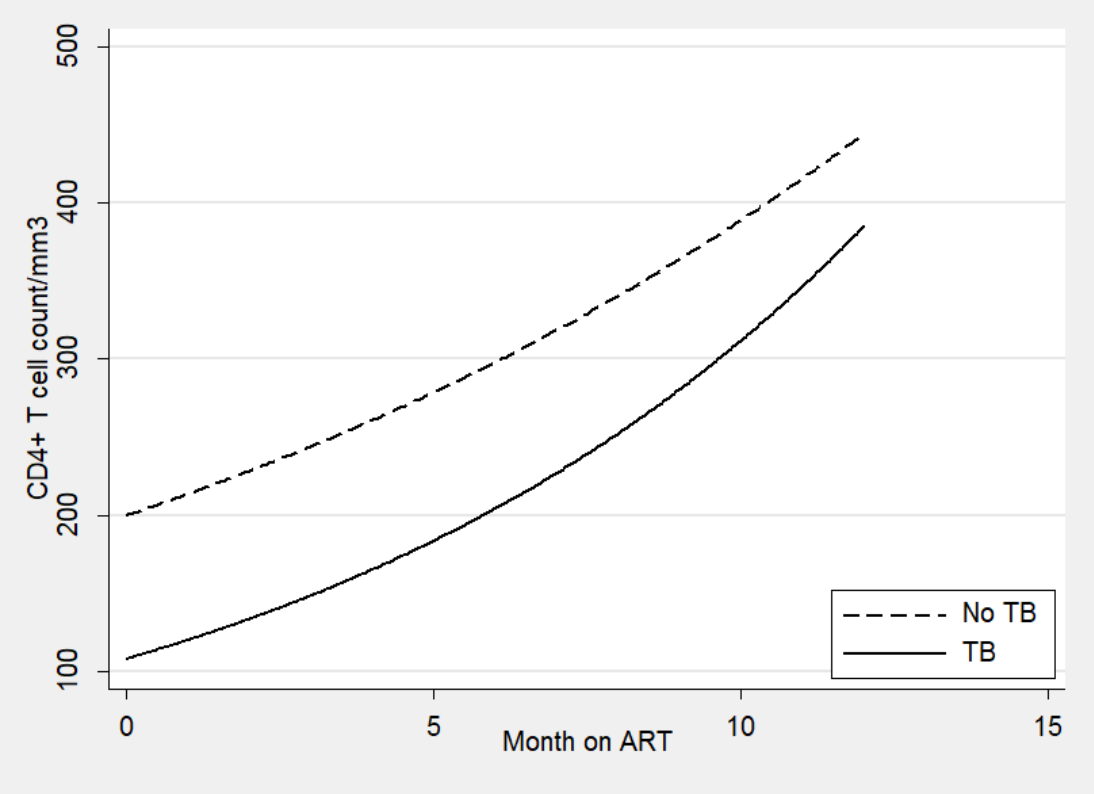
$$\log\left[p(mortality = 1|\, TB,\ Glycemic, Confounders)\right] = \theta_0 + \theta_1 TB + \theta_2 Glycemic + \theta_3 Confounders$$

Linear regression form:

$$\mathrm{E}[Glycemic|\, TB,\ Confounders] = \beta_0 + \beta_1 TB + \beta_2 Confounders$$

β_1= regression coefficient for effect of active TB on glycemic level (mediator). θ_2= regression coefficient for mediator on all-cause mortality. θ_1= regression coefficient for active TB on all-cause mortality controlling for mediator [controlled direct effect]. $\beta_1 * \theta_2$= Natural indirect effect
*p-value <0.05

Figure 3. Estimated CD4 cell count changes of people living with HIV with and without active TB after antiretroviral therapy from the adjusted linear mixed model



CD4 cell counts were back transformed from log CD4

Supplemental table 1. Random intercept model fitting the change of log CD4 counts as a function of active TB disease and time on ART among patients enrolled in the HIV program between 2011-2018 (number of observations=4,411, number of patients=1,561)

Characteristics		Model 1				Model 2			
		Parameter Estimate	**95% Confidence Interval**		**p-value**	**Parameter Estimate**	**95% Confidence Interval**		**p-value**
Fixed Effects			**Lower**	**Upper**			**Lower**	**Upper**	
Intercept		4.97	4.92	5.02	<0.001	5.30	5.12	5.46	<0.001
Active TB	No	Ref				Ref			
	Yes	-0.61	-0.71	-0.51	<0.001	-0.61	-0.71	-0.51	<0.001
Follow up time (months)		0.07	0.06	0.07	<0.001	0.07	0.06	0.07	<0.001
Follow up time* active TB		0.04	0.03	0.05	<0.001	0.04	0.03	0.05	<0.001
Age (year)						-0.01	-0.01	-0.00	<0.001
Sex	Male					-0.06	-0.14	0.02	0.143
	Female					Ref			
Random Effects									
Variance estimates									
Intercept		0.48	0.44	0.53		0.47	0.43	0.52	
Overall Model test									
AIC		9738				9697			
BIC		9776				9748			

TB: tuberculosis, Ref: reference group, AIC: Akaike information criterion, BIC: Bayesian information criterion
Model 1: Adjusted for follow up time and included interaction term between follow up time and active TB
Model 2: Adjusted for follow up time, age and sex and included interaction term between follow up time and active TB

Chapter 4: Paper 3- All-cause mortality associated with hepatitis B and C virus coinfection and hyperglycemia in people living with HIV in Myanmar, 2005-2017 (In progress)

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ABSTRACT

Background: Hepatitis C virus (HCV) and hepatitis B virus (HBV) coinfection are associated with increased mortality in people living with HIV (PLHIV). In addition, diabetes and hyperglycemia are common in PLHIV. Using routinely collected clinical data from PLHIV from Myanmar, we assessed whether associations between HBV/HCV coinfection and all-cause mortality differed by hyperglycemia status.

Methods: Adult PLHIV (≥15 years) from Myanmar who initiated antiretroviral therapy between May 2005 and June 2017 were eligible. HBV and HCV coinfection were measured by hepatitis B surface antigen test and HCV antibody test, respectively, and hyperglycemia by random blood glucose (≥140 mg/dl) at entry to HIV care. Cox proportional hazards models were used to compare all-cause mortality rates in participants by HCV/HBV coinfection and hyperglycemia status.

Results: Among 27,722 PLHIV, 2,260 (8%) had HBV, 2,265 (9%) had HCV, 178 (0.6%) had both HBV/HCV coinfection and 1425 (5%) had hyperglycemia. The overall mortality rate was 3.8 per-100 person-years. The mortality rate among PLHIV with HBV was 4.6, with HCV was 5.1 and with both HBV and HCV was 7.11 per 100-person-years. There was an association between HBV and HCV coinfections and all-cause mortality, and the association between HCV coinfection and all-cause mortality was greater in patients with hyperglycemia [adjusted hazard ratios: 1.58 (95% CI: 1.09, 2.30) for HCV and 3.21 (95% CI: 1.17, 8.84) for HBV/HCV coinfection compared to HIV mono-infection].

Conclusion: Prevention, screening and treatment of chronic HBV and HCV are needed to scale up in this population and clinical guideline to manage hyperglycemia should be developed to reduce mortality.

BACKGROUND

The global progress in reducing HIV-related mortalities is challenged by hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection in people living with HIV (PLHIV). In 2015, the estimated global prevalence of HBV was 7.4% and HCV was 6.2% among PLHIV [192,193]. Cirrhosis and liver cancer due to HBV and HCV are major causes of death globally. Among PLHIV, coinfection with HBV or HCV is associated with increased risk of mortality due to increased risk of chronic liver disease, accelerated liver fibrosis and cirrhosis, and complications that occur in the management of both infections in PLHIV coinfected with HBV or HCV [40,42–45].

Further, type 2 diabetes mellitus (T2DM) is an emerging comorbidity among PLHIV and T2DM comorbidity in PLHIV is associated with increased risk of mortality [68–70]. In addition, T2DM is associated with HCV although the direction and mechanism of the relationship is unknown [122]. Extrahepatic effects of HCV viremia may disrupt endocrine function and glucose homeostasis resulting in increased risk of insulin resistance, hyperglycemia and T2DM [123,125,126]. Most importantly, comorbidities with HBV or HCV and T2DM together may increase the risk of mortality in PLHIV. Preliminary studies suggest that insulin resistance, hyperglycemia, and T2DM are associated with accelerated liver fibrosis, which is the leading cause of liver-death in HBV or HCV coinfected patients [194,195]. However, few studies have examined the risk of mortality associated with HBV and/or HCV in the context of hyperglycemia.

Managing HCV or HBV and hyperglycemia simultaneously is a common and major challenge in many HIV clinical settings. Hence, developing clinical guidelines to manage comorbidities among PLHIV are urgently needed. Given limited information on the relationship

between HBV or HCV coinfection and mortality in the presence of hyperglycemia in PLHIV we aimed to determine 1) the association between HBV and HCV coinfection with all-cause mortality in PLHIV and 2) whether the association between HBV and HCV coinfection with all-cause mortality in PLHIV varied by hyperglycemia status.

METHODS

Study Design

We conducted a retrospective cohort study using data that routinely collected between May 2005 and June 2017 in the Integrated HIV Care program in Myanmar.

Study setting and source of data

Myanmar with an estimated population of 52 million is located in the South-East Asia Region. In 2018, 240,000 people were living with HIV in the country [3]. According to a 2015 prevalence survey, the prevalence of HBV was 6.5% and HCV was 2.7% in the general population [196]. The Integrated HIV Care Program has been implemented jointly by National AIDS Programme and International Union Against Tuberculosis and Lung Disease since 2005 and providing treatment and care to PLHIV in 5 regions/states in Myanmar through 49 clinics. The description of Integrated HIV Care Program was described elsewhere [162]. Briefly, at enrollment to HIV care at the clinic, patients received clinical examination and baseline laboratory investigations including HBV, HCV and tuberculosis (TB) disease screening, CD4 count, hemoglobin and random blood glucose (RBG) measurement. Patients received antiretroviral therapy (ART) and treatment for other opportunistic infections according to National and WHO

HIV clinical guidelines [186,197]. The TDF and lamivudine containing ART regimen which is also active against HBV was widely available since 2011. The chronic HCV treatment using direct-acting antivirals was not available during the study period [198]. Patients were followed up routinely at every three months. Patient outcomes were recorded as regular follow-up (attending clinic appointment regularly), death (patient's family or the outreach workers reported to the clinic that the patient had died), lost to follow-up (not attending the clinic within three months after the scheduled appointment date) and transfer out (patient was transferred out to other HIV care program). Date of death was recorded from hospital records if patients died at the hospital or as reported by families if the patient died at home. At every visit, patients' data were recorded on paper-based patient medical records by medical officers and entered into an electronic database by data entry operators. For this study, data of patients who initiated ART between 1st May 2005 and 31st June 2016 with their follow-up and outcome data until 31st June 2017 were extracted from the electronic database.

Study participants

PLHIV aged ≥15 years who initiated ART between May 2005 and June 2016 and who were tested for HBV and/or HCV coinfection at enrollment to HIV care were eligible. PLHIV whose HBV and HCV status were not known were excluded.

Study variables

The primary exposure variables was HBV and/or HCV coinfection status which was extracted from patients' medical records. As standard of care, hepatitis screening is performed for all patients at the time enrollment to HIV care. HBV infection status was measured using Hepatitis B surface antigen (HBsAg) (Alere Determine™) and HCV infection measured by HCV antibody

testing (OraQuick® immunoassay). HBV and/or HCV infection status was categorized as HIV mono-infection if the patient was not tested positive for both HBV and HCV, HBV coinfection if the patient was tested positive for HBV only, HCV coinfection if the patient was tested positive for HCV only and both HBV and HCV coinfection if the patient was tested positive for both HBV and HCV.

The primary outcome was all-cause mortality defined as death due to any cause between the date of ART initiation and 30th June 2017 (the end of follow-up). All-cause mortality status was determined from patients' medical records.

Covariates included age, gender, alcohol drinking, body mass index (BMI), CD4 cell count, WHO clinical staging, anemia and hyperglycemia at enrollment to HIV care and calendar year of ART initiating. RBG ≥140 mg/dl was defined as hyperglycaemia according to previous studies and WHO 2-hour postprandial blood glucose classification for diagnosis of prediabetes [164–166]. RBG was measured at enrolment by glucometer using capillary blood. Alcohol drinking status was based on self-reported drinking habit at the time of enrollment. BMI was calculated from enrollment weight and height. BMI and anemia were categorized according to WHO guidelines for Asian populations [163,199]. Anemia was categorized based on hemoglobin (mg/dl) levels: normal (male, ≥13 g/dl; female, ≥12 g/dl), mild (male, 11–12.9 g/dl; female, 11–11.9 g/dl), moderate (both sexes, 8.0–10.9 g/dl) and severe anemia (both sexes <8.0 g/dl). Calendar year of ART initiation was dichotomized into the period before (1st May 2005 to 31st December 2010) and after (1st January 2011 to 30th June 2016) TDF was widely available.

Analysis and statistics

Numbers and proportions were used to summarize the prevalence of HBV and HCV coinfection and the characteristics of the study cohort. All-cause mortality rates (per 100 person-years of follow-up) were calculated for four groups: HIV mono-infection, HBV coinfected, HCV coinfected and HBV-HCV coinfected. Follow-up person-time was calculated from the date of ART initiation to date of all-cause mortality, loss to follow-up, or end of follow-up period (30th June 2017). We compared mortality rate differences in coinfected patients compared to the HIV mono-infection group. Kaplan-Meier survival curves were plotted from time to ART initiation to all-cause mortality stratified by HBV and/or HCV coinfection status. We used Cox proportional hazard models to estimate hazard ratios (HR) with 95% confidence interval (CI) to determine the association of HBV and/or HCV coinfection with all-cause mortality. Proportional hazard assumptions were assessed using log-log plots and Schoenfeld residuals [200]. The variables for which the proportional hazard assumption did not hold were included as a time varying covariate in the model. Final models were adjusted for potential confounders based on directed acyclic graph theory [201] and observed characteristics associated with exposure (HBV and/or HCV coinfection) and outcome (all-cause mortality) in bivariate analysis. We stratified the Cox proportional hazard models by hyperglycemia status to determine whether the association between HBV and HCV coinfection with all-cause mortality in PLHIV varied by hyperglycemia status. Sensitivity analyses were performed to account for bias due to 1) exposure misclassification by estimating relative risk using different sensitivities and specificities of the measurement, 2) outcome misclassification by fitting the Cox models after reclassified the patients who were loss to follow-up as deaths, and 3) unknown confounders by calculating e-values [167,168]. All analysis was performed using STATA version 14.2 (College Station, TX, USA).

Ethics approval

The ethics approval was obtained from the Ethics Advisory Group of The Union, Paris, France (EAG/53/17), the ethical review committee of the Department of Medical Research, Ministry of Health and Sports, Myanmar (Ethics/DMR/2018/053) and Institutional Review Board at Georgia State University (H18392). We also obtained permission to conduct the study from the National AIDS Programme, Myanmar.

RESULTS

During the study period, 31,047 PLHIV initiated ART and 27713 (89%) patients tested for HBV and 27,690 (89%) tested for HCV. Of 27,722 patients eligible for this study, 2260 (8%) were HBV positive, 2265 (8%) were HCV positive and 178 (0.6%) were both HBV and HCV positive **(Figure 1)**. The median age was 35 years (interquartile range: 30-42), 57% of patients were male, 5% had hyperglycemia (RBG ≥140 mg/dl), 36% had BMI <18.5 kg/m^2 and 59% had CD4 <200 cell/mm^3) **(Table 1)**.

Patient characteristics and the proportion of HBV, HCV or both HBV and HCV coinfection are presented in **Table 1.** The prevalence of HCV coinfection was higher in patients older than 45 years compared to those in younger age groups (11% vs 8%), in male patients compare to female (11% vs 5%), in patient with hyperglycemia compared to euglycemia (12% vs 8%) and in social or habitual alcohol drinkers compared to those who never drunk (10% and 13% vs 6%).

Patient characteristics associated with all-cause mortality

A total of 27,722 patients contributed to 96,994 person-years was included in this analysis. During the median follow-up of 3.1 years (IQR 1.5 – 5.1 years), 3655 (13%) patients died and the

overall mortality rate was 3.8 (95% CI:3.7, 3.9) per 100 person-years **(Table 2)**. Patients who were older than 45 years [HR:1.98, 95% CI:1.67, 2.35], were male [HR: 1.83, 95% CI: 1.71, 1.97], had hyperglycemia [HR: 1.33, 95% CI 1.17, 1.52], were habitual drinker [HR: 1.87, 95% CI: 1.69, 2.06], had BMI <18.5 [HR: 1.82, 95% CI: 1.68, 1.97], CD4 count <200 cell/mm [HR: 33.24, 95% CI:2.84, 3.70] , had severe anemia [HR: 4.88, 95% CI:4.34,5.49], and had tuberculosis disease [HR: 1.75, 95% CI:1.64,1.87] had a higher hazard rate of all-cause mortality **(Table 2)**.

Association between HBV and/or HCV coinfection and all-cause mortality

The cumulative survival among those with HBV and HCV coinfection was lower compared to those with HIV mono-infection (log-rank *p*-value < 0.001) **(Figure 2)**.

The mortality rate among PLHIV coinfected with HBV was 4.6, with HCV was 5.1 and with HBV and HCV was 7.7 per 100 person-years. The adjusted HR of all-cause mortality among PLHIV with HBV coinfection was 1.25 (95% CI:1.11,1.40), among those with HCV coinfection it was 1.52 (95% CI: 1.35,1.71), and among those with both HBV and HCV coinfection was 2.14 (95% CI: 1.51, 3.02) compared to HIV mono-infection group **(Table 3)**.

When stratified by hyperglycemia status, the association between HCV coinfection and mortality was greater among patients with hyperglycemia. Among patients with euglycemia, the adjusted HR for patients with HCV coinfection was 1.44 [95% CI: 1.24, 1.66] and for those with both HBV and HCV coinfection was 1.78 [(5 % CI: 1.14, 2.77] compared to HIV mono-infection group. Among patients with hyperglycemia, the adjusted HR for patients with HCV infection was 1.85 [95% CI: 1.23, 2.78] and for those with both HBV and HCV coinfection was 4.39 [95% CI: 1.51, 12.76] **(Table 3)**.

Sensitivity analyses

To assess the potential misclassification of HBV and/or HCV coinfection, we calculated relative risks (RR) of mortality associated with HBV and/or HCV coinfection using sensitivity and specificity of measurement range from .80 to .99. Compared to HIV mono-infection, the observed RR among HBV coinfection was 1.27, among HCV coinfection was 1.43 and HBV and HCV coinfection was 2.17. From the sensitivity analysis, the point estimate of RRs range from 0.31 to 1.38 among HBV coinfection, 0.28 to 1.60 among HCV coinfection and 0.18 to 2.63 among HBV and HCV coinfection. When patients who were lost to follow-up from the program were reclassified as having died and included in the all-cause mortality group, the association between hepatitis coinfection and all-cause mortality remained significant, with a similar effect size [aHR: 1.19, 95% CI: 1.09, 1.32 for HBV coinfection, aHR: 1.46, 95% CI: 1.32, 1.60 for HCV coinfection and aHR: 2.36, 95% CI: 1.82, 3.06 for HBV and HCV coinfection]. The e-value for the association between risk of mortality with HBV coinfection and was 1.61, with HCV coinfection was 2.01 and with both HBV and HCV coinfection was 2.77 showing that only if there is a strong association between unmeasured confounder with both exposure and outcome could shift our observed association toward null.

DISCUSSION

This study addressed the association between HBV and/or HCV coinfection with all-cause mortality stratified by hyperglycemia status in a large cohort of PLHIV on ART. We found that the prevalence of HBV or HCV coinfection was high in this PLHIV cohort: approximately 9% were HBV or HCV serology positive at enrollment to HIV care. Our study also demonstrated that

coinfection with HBV and/or HCV increased the risk of mortality. The mortality in PLHIV with HBV coinfection was 20% higher at any given point in time compared to PLHIV without hepatitis coinfection. The mortality among PLHIV with HCV coinfection was 50% higher and among PLHIV compared to those without hepatitis coinfection. Among PLHIV with both HBV and HCV coinfection, the hazard of mortality was two-fold higher compared to those without hepatitis coinfection. Importantly, we found that the relationship between HBV and/or HCV coinfection and mortality varied by patient's hyperglycemia status. The risk of mortality among HCV coinfected or both HBV and HCV coinfected PLHIV was greater in hyperglycemic group. However, the risk of mortality among HBV coinfected PLHIV was greater in euglycemic group.

The prevalence of HBV in this cohort is similar to the prevalence found in a previous study conducted in 2012 in the same IHC program [202]. However, the prevalence of HCV coinfection was higher in this study compared to the previous study (9% vs 5%). This may be due to the enrollment of patients who were at higher risk of HCV coinfection, such as patients who were using injection drugs, engaging in sex work, and men who had sex with men to the program after 2012. The prevalence of HCV coinfection found in our study was in a higher range compared to that has been reported in a global meta-analysis (2.4%; IQR: 0.8 to 8.4) [38] and was similar to the prevalence of HCV (9.5%) among a male PLHIV cohort enrolled between 2004 and 2014 from a private HIV care clinic in Myanmar supported by Médecins Sans Frontiers [203].

PLHIV with HBV and/or HCV had a higher risk of mortality in this cohort. Our findings are commensurate with data from other countries and settings where treatment for HBV or HCV coinfection is not available [40,43,44,204–207]. Most importantly, patients coinfected with both HBV/HCV had the highest risk of mortality, with a two-fold increase in the overall mortality rate

compared to PLHIV without hepatitis virus coinfection. This is similar to other studies which showed that dual HBV/HCV coinfection substantially increased the mortality in PLHIV [42,207].

There are growing evidence that HCV coinfection and T2DM together increase the risk of mortality in PLHIV. As many studies suggested, patients with HIV/HCV co-infection are at increased risk of metabolic syndrome including T2DM and predispose to poor clinical outcomes [124,208,209]. A cohort study from Italy reported that among HCV coinfected PLHIV, T2DM was associated with 3-fold risk of liver-related deaths compared to those without T2DM [123]. There are also growing evidence suggestion that treatment of HCV can improve the metabolic complications [210]. However, HCV treatment was not available in Myanmar during the study period which could contributed to increased mortality among HCV coinfected PLHIV with hyperglycemia. HCV treatment in PLHIV started available in some cities in 2017 and future studies should be planned to assess the association of HCV treatment with mortality in PLHIV with hyperglycemia or diabetes mellitus.

One of the strengths of this study is the use of a large PLHIV cohort that covers one third of PLHIV receiving care in Myanmar in the public health sector, and our results are therefore generalizable to PLHIV in Myanmar. In addition, we had information on date of exposure and outcomes, which allowed us to perform time to event analysis to provide robust estimates of the effect of exposure on mortality.

There are some limitations in this study. First, we defined exposure (HBV and/or HCV coinfection status) based on HBs antigen and HCV antibody serology tested at enrollment to the HIV clinic which only provided the acute infection status. About 90% of acute HBV and 50% of acute HCV infection can naturally resolve. Investigations for chronic HBV or HCV status were

not available in this setting. Hence, we could not differentiate between acute, chronic or resolved coinfection. In addition, our data did not capture those who acquired coinfection during follow-up. Further, there could be few patients who received treatment from HCV in private clinic and we did not have information of them. Hence, we cannot make conclusion on whether mortality risk we found is associated with acute or chronic infection.

Second, we defined hyperglycemia based on RBG level which has limited validity to assess patient's glycemic status. This may introduce bias due to misclassification of covariates and may shift our estimates toward or away from null. It is also possible that the misclassification of hyperglycemia status can be differential with respect to mortality. Patients who were very sick may not have enough food and the RBG measurement would capture the low level of glycemia or patients who were very sick may have stress response and the RBG measurement would capture the high level of glycemia. We also cannot identify whether those with hyperglycemia were diagnosed diabetes mellitus or not due to lack of screening and recording.

Third, 11% of PLHIV were not tested for hepatitis and thus were excluded from the study. The characteristics of patients who were excluded and included in the analysis were different. Assuming missingness is missing at random, missingness is not monotone and, sex, alcohol consumption, CD4, BMI and anemia as auxiliary variables, we performed multiple imputation using chained equations and estimated the hazard ratios. The HRs for all the models provide similar results. However, if the missingness is not at random, selection bias can still be present.

Despite the limitations, there are some public health and clinical implications from this study. First, the prevalence of HBV and HCV coinfection in PLHIV was high in this setting. Accordingly, public health interventions to reduce new hepatitis infections such as HBV

vaccination and harm reduction program should be strengthened for PLHIV to reduce mortality among PLHIV. Reducing coinfection is critical as evidence suggests that even after HBV treatment was available and used as part of the ART regimen, PLHIV with HBV coinfection experienced an increased risk of death compared to those without HBV coinfection [211]. HBV vaccination among those who did not have HBV infection is a recommended strategy in addition to health education and harm reduction among those who have a high risk of HBV infection [39,196].

Second, harm reduction prevention programs to reduce HCV infection, especially in high-risk groups, should be strengthen. Third, as HCV coinfection significantly increased mortality among PLHIV, HCV treatment for coinfected patients should be scaled up for the whole country. The newer direct-acting antiviral agents for HCV virus have demonstrated promising results for HIV/HCV coinfected patients and have been shown to decrease mortality among PLHIV [212,213]. In addition, the association between HCV and mortality was higher in PLHIV with hyperglycemia. Hence, clinical guidelines should be developed for screening and management of hyperglycemia and diabetes mellitus for PLHIV with HCV coinfection in this setting. Finally, testing and recording of chronic HBV and HCV status among PLHIV and monitoring the effect of HBV and HCV treatment on HIV clinical outcomes would add to the evidence base towards improving the clinical management of HBV and HCV among PLHIV.

CONCLUSIONS

This study demonstrated a high prevalence of HBV and HCV coinfection among PLHIV and a higher mortality among those coinfected by either HBV or HCV and hyperglycemia. In

addition to HBV and HCV screening at enrollment to HIV care, chronic HBV and HCV status should be assessed by regularly testing HBV and HCV during follow-up along with HBV panel and HCV RNA testing among those HBV and/or HCV screening positive to better understand the impact of HBV and HCV coinfection on patients' outcomes. Finally, the treatment for HCV coinfected patients should be scaled up to reduce mortality.

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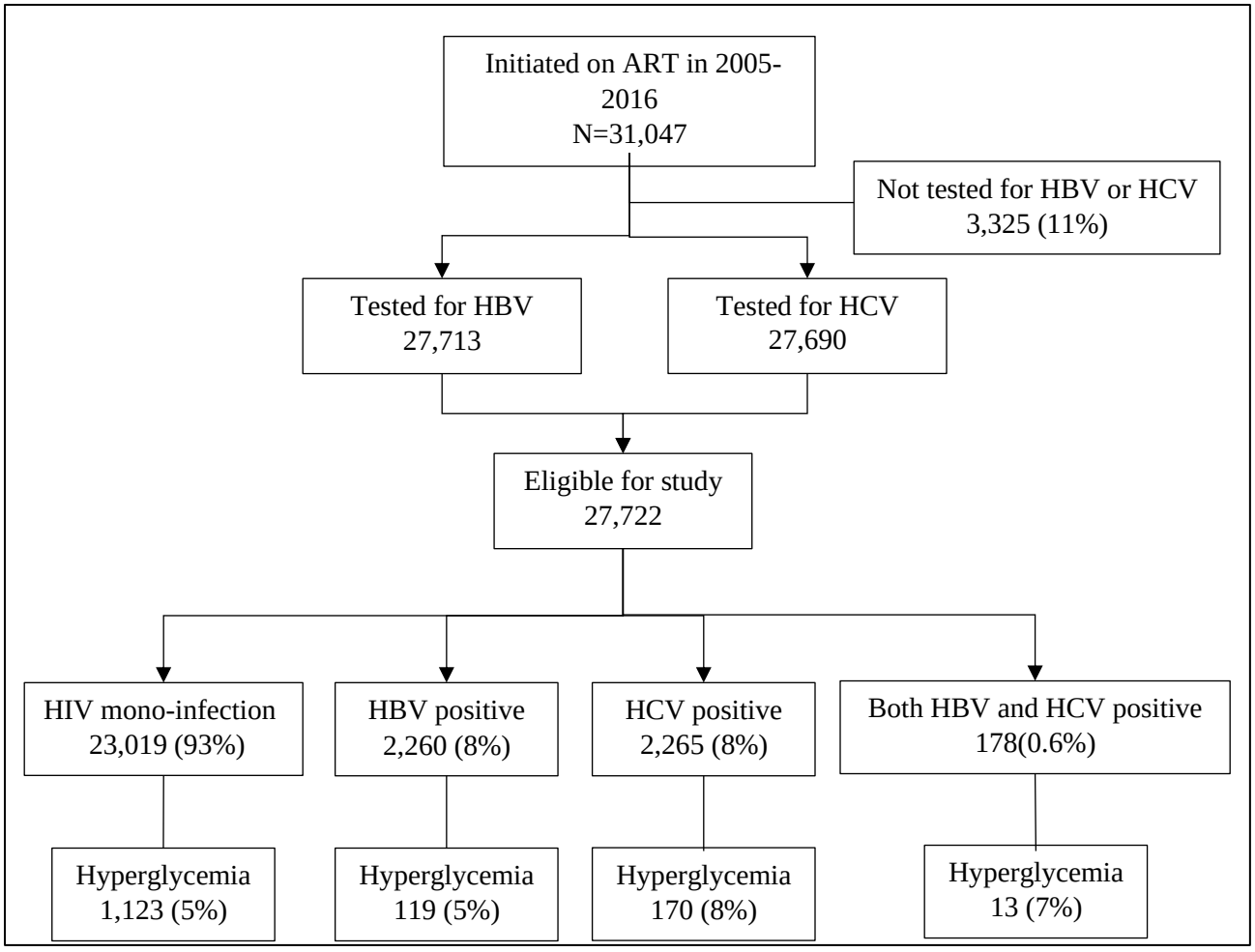
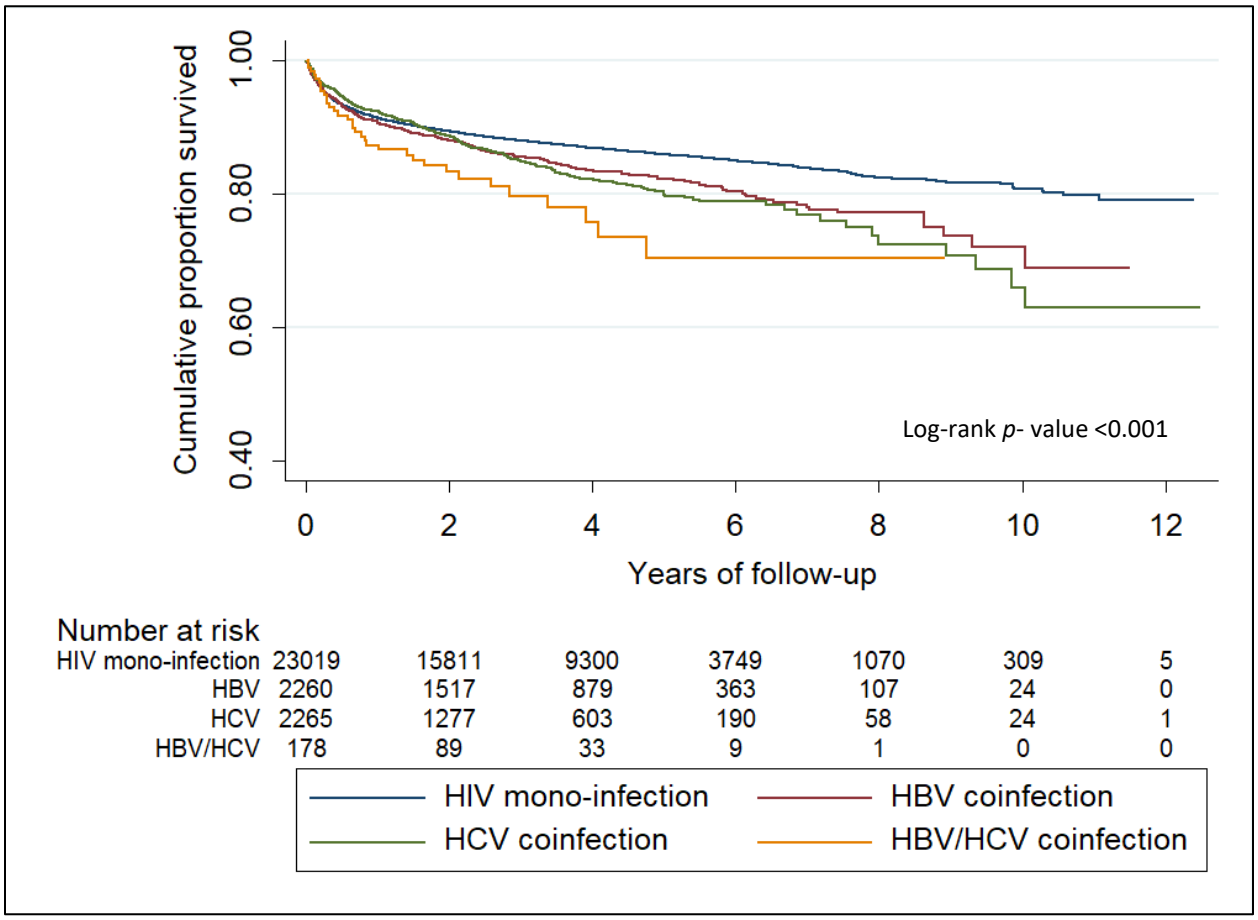
Figure 1. Flow diagram of the people living with HIV initiated on ART under Integrated HIV Care Program in Myanmar 2005-2016 stratified by their baseline HBV and/or HCV coinfection and hyperglycemia status



ART: antiretroviral therapy; HBs: hepatitis B surface; HCV: hepatitis C virus; Hyperglycemia: random blood glucose ≥140 mg/dl

Figure 2. Kaplan-Meier survival curve stratified by hepatitis B and/or C coinfection status among people living with HIV initiated on ART between 2005 and 2017 in Integrated HIV Care program in Myanmar



HBV: hepatitis B virus; HCV: hepatitis C virus

Table 1. Demographic, clinical and treatment characteristics at enrollment of people living with HIV who initiated on antiretroviral therapy under the Integrated HIV Care Program, Myanmar, 2005-2016 by HBV and/or HCV coinfection status (N=27,722)

	Total		HIV mono-infection n=23,019		HBV n=2,260		HCV n=2,265		HBV and HCV n=178	
Characteristics	n	(%)≠	n	(%)©	n	(%)©	n	(%)©	n	(%)©
Age in years										
Median (IQR)	35	(30, 42)	35	(30, 41)	35	(30, 41)	35	(30, 43)	35	(30, 40)
15-24	1,838	(7)	1,537	(84)	135	(7)	156	(9)	10	(1)
25-45	21,887	(79)	18,207	(83)	1,851	(9)	1,686	(8)	143	(1)
>45	3,997	(14)	3,275	(82)	274	(7)	423	(11)	25	(1)
Gender										
Male	15,764	(57)	12,385	(79)	1,538	(10)	1,699	(11)	142	(1)
Female	11,958	(43)	10,634	(89)	722	(6)	566	(5)	36	(<1)
Random blood glucose level mg/dl										
Median (IQR)	90	(76,106)	88	(75, 106)	90	(76, 107)	94	(77, 114)	95	(79, 118)
Euglycemia (<140)	20,428	(74)	16,959	(83)	1,676	(8)	1,659	(8)	134	(1)
Hyperglycemia (≥140)	1,425	(5)	1,123	(79)	119	(8)	170	(12)	13	(1)
Not recorded	5,869	(21)	4,937	(84)	465	(8)	436	(7)	31	(1)
Alcohol drinking										
Never	18,386	(66)	15,863	(86)	1,299	(7)	1,140	(6)	84	(1)
Habitual (daily)	2,370	(9)	1,834	(77)	278	(12)	242	(10)	16	(1)
Social (occasionally)	6,145	(22)	4,627	(75)	623	(10)	821	(13)	74	(1)
Not recorded	821	(3)	695	(85)	60	(7)	62	(8)	4	(1)
BMI (kg/m^2)										

	Median (IQR)	19	(17,22)	19	(17,22)	19	(17,21)	19	(18,22)	21	(18, 22)
	<18.5	9,970	(36)	8,342	(84)	858	(9)	725	(7)	45	(1)
	18.5-22.9	9,853	(36)	7,920	(80)	829	(8)	1,018	(10)	86	(1)
	23.0-27.5	3,363	(12)	2,821	(84)	245	(7)	273	(8)	26	(1)
	>27.5	1,599	(6)	1,421	(89)	113	(7)	63	(4)	2	(<1)
	Not recorded	2,933	(11)	2,515	(86)	215	(7)	186	(6)	19	(1)
WHO clinical staging											
	1 or 2	11,192	(40)	9,342	(84)	820	(7)	954	(9)	76	(1)
	3 or 4	16,519	(60)	13,667	(83)	1,440	(9)	1,310	(8)	102	(1)
	Not recorded	11	(<1)	10	(91)	0	(0)	1	(9)	0	(0)
CD4 count (cell/mm^3)											
	Median (IQR)	158	(72,287)	154	(70, 284)	149	(70, 274)	201	(104, 329)	209	(116,337)
	>350	4,668	(17)	3,816	(82)	335	(7)	476	(10)	41	(1)
	200-349	6,522	(24)	5,289	(81)	523	(8)	657	(10)	53	(1)
	<200	16,323	(59)	13,741	(84)	1,380	(9)	1,120	(7)	81	(1)
	Not recorded	210	(1)	173	(82)	22	(11)	12	(6)	3	(1)
Anemia											
	No anemia	8,566	(31)	6,879	(80)	686	(8)	925	(11)	76	(1)
	Mild to Moderate	16,610	(60)	13,964	(84)	1,375	(8)	1,184	(7)	87	(1)
	Severe	2,088	(8)	1,798	(86)	155	(7)	123	(6)	12	(1)
	Not recorded	458	(2)	378	(83)	44	(10)	33	(7)	3	(1)
Tuberculosis disease											
	No	19,452	(70)	16,171	(83)	1,516	(8)	1,634	(8)	131	(1)
	Yes	8,270	(30)	6,848	(83)	744	(9)	631	(8)	47	(1)
Initiated on TDF and lamivudine											
	No	14,100	(51)	12,344	(88)	725	(5)	992	(7)	39	(<1)
	Yes	13,622	(49)	10,675	(78)	1,535	(11)	1,273	(9)	139	(1)

Col: column, IQR: interquartile range, BMI: body mass index, TDF: tenofovir disoproxil fumarate

≠ Column percentage, © Row percentage of total

¥ Patients who received TB treatment at enrollment to HIV care or started TB treatment within 90 days of enrollment to HIV care

Table 2. Demographic, clinical and treatment characteristics at enrollment associated with all-cause mortality among people living with HIV who initiated on antiretroviral therapy under the Integrated HIV Care Program, Myanmar, 2005-2016 (N=27,722)

			All-cause mortality	
Characteristics	Person-years	n	Rate [95% CI]	HR [95% CI]
Total				
Age in years	96,994	3655	3.8 [3.7, 3.9]	
<25	5813	161	2.8 [2.4, 3.2]	Ref
25-45	78545	2813	3.6 [3.5, 3.7]	**1.4 [1.19,1.64]**
>45	12637	681	5.4 [5, 5.8]	**1.98 [1.67,2.35]**
Gender				
Male	54248	2562	4.7 [4.5, 4.9]	**1.83 [1.71,1.97]**
Female	42747	1093	2.6 [2.4, 2.7]	Ref
Random blood glucose level				
Euglycemia (<140)	66841	2681	4 [3.9, 4.2]	Ref
Hyperglycemia (≥140)	4464	241	5.4 [4.8, 6.1]	**1.33 [1.17, 1.52]**
Not recorded	25690	733	2.9 [2.7, 3.1]	**0.84 [0.77, 0.91]**
Alcohol drinking				
Never	66242	2179	3.3 [3.2, 3.4]	Ref
Habitual (daily)	7635	491	6.4 [5.9, 7]	**1.87 [1.69,2.06]**
Social (occasionally)	19185	897	4.7 [4.4, 5]	**1.32 [1.22,1.42]**
Not recorded	3932	88	2.2 [1.8, 2.8]	**0.80 [0.64,0.99]**
BMI category				
<18.5	37524	1748	4.7 [4.4, 4.9]	**1.82 [1.68,1.97]**
18.5-22.9	36489	959	2.6 [2.5, 2.8]	Ref
23-27.5	11700	208	1.8 [1.6, 2]	**0.65 [0.56,0.75]**
>27.5	4453	100	2.2 [1.8, 2.7]	**0.71 [0.58,0.88]**
Not recorded	6829	640	9.4 [8.7, 10.1]	**2.84 [2.57,3.14]**
Baseline WHO staging				
1 or 2	36927	704	1.9 [1.8, 2.1]	Ref

	3 or 4	60022	2949	4.9 [4.7, 5.1]	**2.83**	**[2.60, 3.07]**
	Not recorded	46	2	4.4 [1.1, 17.5]	2.95	[0.74, 11.81]
Baseline CD4 count (cell/mm3)						
	>350	14804	239	1.6 [1.4, 1.8]		Ref
	200-349	23035	499	2.2 [2, 2.4]	**1.43**	**[1.23,1.67]**
	<200	59000	2774	4.7 [4.5, 4.9]	**3.24**	**[2.84,3.70]**
	Not recorded	156	143	91.4 [77.6, 107.7]	**34.54**	**[28.05,42.54]**
Anemia						
	No anemia	29207	533	1.8 [1.7, 2]		Ref
	Mild to Moderate	59845	2486	4.2 [4, 4.3]	**2.41**	**[2.19,2.64]**
	Severe	6407	566	8.8 [8.1, 9.6]	**4.88**	**[4.34,5.49]**
	Not recorded	1535	70	4.6 [3.6, 5.8]	**2.64**	**[2.05,3.38]**
Tuberculosis disease[¥]						
	No	65575	2070	3.2 [3, 3.3]		Ref
	Yes	31420	1585	5 [4.8, 5.3]	**1.75**	**[1.64,1.87]**
Initiated on TDF and lamivudine						
	No	66265	2105	3.2 [3, 3.3]		Ref
	Yes	30730	1550	5 [4.8, 5.3]	**1.02**	**[0.95,1.09]**

Ref: reference group, BMI: body mass index, TDF: tenofovir disoproxil fumarate

[¥] Patients who received TB treatment at enrollment to HIV care or started TB treatment within 90 days of enrollment to HIV care.

Bold indicates 95% confidence interval estimate did not include null value.

Table 3. Association between HBV and/or HCV coinfection and all-cause mortality among people living with HIV who initiated on antiretroviral therapy under the Integrated HIV Care Program, Myanmar, 2005-2016

			All-cause mortality								
	Number	**Person-years**	**n**	**Rate¥**	**[95% CI]**	**HR€**	**[95% CI]**		**aHR€***	**[95% CI]**	
All patients											
Total	27,722	96,994	3655	3.8	[3.7, 3.9]						
HIV mono-infection	23,019	82,184	2932	3.6	[3.4, 3.7]	Ref			Ref		
HBV	2,260	7,885	358	4.6	[4.1, 5.1]	**1.37**	**[1.23,**	**1.54]**	**1.25**	**[1.11,**	**1.40]**
HCV	2,265	6,498	332	5.1	[4.6, 5.7]	**1.50**	**[1.33,**	**1.69]**	**1.52**	**[1.35,**	**1.71]**
HBV and HCV	178	428	33	7.7	[5.5, 10.9]	**2.27**	**[1.61,**	**3.21]**	**2.14**	**[1.51,**	**3.02]**
Patients with euglycemia (RBG <140mg/dl)											
Total	20,428	66841	2681	4.0	[3.9, 4.2]						
HIV mono-infection	16,959	56557	2160	3.8	[3.7, 4.0]	Ref			Ref		
HBV	1,676	5444	274	5.0	[4.5, 5.7]	**1.43**	**[1.26**	**1.62]**	**1.28**	**[1.12,**	**1.46]**
HCV	1,659	4512	227	5.0	[4.4, 5.7]	**1.39**	**[1.21,**	**1.61]**	**1.44**	**[1.24,**	**1.66]**
HBV and HCV	134	328	20	6.1	[3.9, 9.5]	**1.72**	**[1.11,**	**2.69]**	**1.78**	**[1.14,**	**2.77]**

Patient with hyperglycemia (RBG ≥140 mg/dl)												
Total	1,425	4464	241	5.4	[4.8,	6.1]						
HIV mono-infection	1,123	3,706	181	4.9	[4.2,	5.7]	Ref			Ref		
HBV	119	387	21	5.3	[3.5,	8.3]	1.16	[0.73,	1.83]	0.95	[0.59,	1.51]
HCV	170	356	35	9.8	[7.1,	13.7]	**1.79**	**[1.19,**	**2.67]**	**1.85**	**[1.23,**	**2.78]**
HBV and HCV	13	16	4	25.6	[9.6	68.3]	**4.22**	**[1.50,**	**11.93]**	**4.39**	**[1.51,**	**12.76]**

HR: hazard ratio; aHR: adjusted HR; HBV: hepatitis B virus; HCV: hepatitis C virus, Ref: reference group

¥ Rate per 100 person-years follow-up

€ proportional hazard assumption did not hold for the exposure variable and included as a time varying covariate in the model

*adjusted for age, gender, alcohol drinking history, body mass index, CD4+ T cell count, anemia, and tuberculosis disease at enrollment, initiated on TDF plus lamivudine regimen or not, and year of ART initiation

Likelihood ratio p-value for statistical interaction term between HBV and/or HCV coinfection and hyperglycemia status = 0.09

Chapter 5: Summary and Future Directions in Research

5.1 Overview of findings

Overall, the findings from the three studies suggests that comorbidities with chronic infectious diseases – TB, HBV and HCV and non-infectious comorbidity – hyperglycemia in PLHIV is associated with poor clinical outcomes.

The results of the study 1 suggested that there is a biological interaction between low BMI and hyperglycemia on the risk of TB disease among PLHIV. Study 1 included 20,865 PLHIV enrolled in 49 HIV clinics in Myanmar between 2011 and 2017. In this cohort, the median age was 36 years (range 15-91 years), 11,538 (55%) were male, 7,610 (36%) had low BMI, 1,324 (6%) had hyperglycemia. During the median follow-up of 2.2 (IQR: 0.5-4.2), 3,628 (17%) developed active TB and the incidence rate of active TB was seven cases per 100 person-years. From the adjusted Cox proportional hazards model, we observed that the hazard rate of incident TB among PLHIV with joint exposure was 1.84 times compared to those with no exposure (95% CI: 1.55, 2.18). There was a biological interaction between two exposure (synergy index: 2.01, 95% CI: 1.09, 3.74), the relative excess risk (of TB disease) due to the interaction of two exposures was 0.42 (95% CI:0.07, 0.78) and the attributable proportion to the risk of TB due to joint exposure was 23%.

The results of the study 2 showed that one in five PLHIV in the study cohort had prevalent of TB and 21% of the PLHIV in the cohort died during one year of follow-up. PLHIV with active TB experienced higher mortality and lower CD4 cell counts compared to PLHIV without TB. PLHIV with active TB experienced similar CD4 cell count increase as in their counterpart once they were initiated on ART. This study included 1,871 adult PLHIV enrolled in one outpatient

HIV clinic in Myanmar between 2011 and 2018. In this cohort, 687 (37%) had CD4 cell count <100 cell/mm3 and 394 (21%) had active TB within 90 days of enrollment to HIV care. The median random blood glucose level was 86 mg/dl (interquartile range: 74, 99). One-year all-cause mortality was significantly associated active TB [adjusted relative risk:1.75, 95% CI:1.38, 2.21]. The mean log CD4 cell count during the follow-up was significantly lower in PLHIV with active TB compared to those without active TB [βTB = -0.61, 95% CI: -0.71, -0.51, βTB*follow-up month= 0.04, 95% CI: 0.03, 0.05]. However, we did not observe clinically meaningful role of glycemic level as a mediator in the relationship between active TB and all-cause mortality

The results of the study 3 suggests that PLHIV coinfected with HBV or HCV experienced higher rates of mortality and the mortality was greater among those comorbid with hyperglycemia. This study used cohort data of 27,722 adult PLHIV enrolled in 49 HIV clinics in Myanmar between 2005 and 2016. Among them, 2,260 (8%) had HBV, 2,265 (9%) had HCV, 178 (0.6%) had both HBV/HCV coinfection and 1425 (5%) had hyperglycemia. During the median follow-up of 3.1 years (IQR 1.5 – 5.1), 3655 (13%) patients died and the overall mortality rate was 3.8 (95% CI:3.7,3.9) per 100 person-years. There was a significant association between hepatitis virus coinfections and all-cause mortality [adjusted HR: 1.25 (95% CI:1.11,1.40) for HBV, 1.52 (95% CI: 1.35,1.71) for HCV and 2.14 (95% CI: 1.51, 3.02) for HBV/HCV coinfection]. The association was stronger in patients with hyperglycemia [adjusted hazard ratios: 1.58 (95% CI: 1.09, 2.30) for HCV and 3.21 (95% CI: 1.17, 8.84) for HBV/HCV coinfection compared to HIV mono-infection].

5.2 Public health and clinical implications

The findings of this dissertation project have many public health and clinical implications. From study 1, we identified the PLHIV subgroup which has the highest risk of TB disease.

Identification of subgroups with a high risk of TB disease is important to effectively allocate the public health resources to target the intervention to reduce TB incidence. As Myanmar is a resource-limited country, intervention to prevent TB disease such as providing isoniazid therapy should be prioritized for the group with the highest risk. In addition, interventions such as providing a nutritional supplementation to improve weight gain and diagnosis and treatment of hyperglycemia and T2DM to reduce the risk of TB disease in PLHIV especially among joint exposure group should be considered. In addition, we observed that habitual alcohol consumption was associated with underweight and risk of TB disease. Hence, HIV program should consider investing resources for patient counselling to reduce alcohol use to prevent adverse clinical outcomes.

Findings from study 2 highlighted a high prevalence of TB in PLHIV, the adverse clinical outcomes in PLHIV with TB comorbidity and deficiency of T2DM screening and viral load testing or recording in HIV program. As patients with active TB disease had a higher mortality, TB preventive interventions should be urgently implemented in this setting. In addition, PLHIV with active TB in our study showed decent CD4 count increase once they were on both ART and TB treatment. Hence, PLHIV should be screened for early diagnosis and treatment active TB as well as initiated on ART early to prevent mortality related to severe immunodeficiency. In this setting, fasting blood glucose or HbA1c is not routinely used to screen T2DM. High RBG level was associated with mortality in this study, the HIV management clinical guideline should include screening of T2DM and management of hyperglycemia in Myanmar. However, the role of glycemia in TB/HIV related mortality and the optimal timing and level of blood glucose level in TB and HIV coinfection are unknown, caution should be made in control of hyperglycemia. The viral load testing is low in this study site and needs to be increased to assess the actual prevalence

of virological failure. One of the reasons is because the study site does not have viral load testing facilities and the closet viral load testing facility is about 200 miles away and required blood sample transportation. HIV program needs to develop strategy to improve access to T2DM screening and viral load testing in PLHIV.

Study 3 demonstrated a high prevalence of HBV and HCV coinfection among PLHIV and a higher mortality among those coinfected by either HBV or HCV and hyperglycemia in Myanmar. Accordingly, national public health programs should implement or strengthen public health interventions to reduce new hepatitis infections to reduce mortality among PLHIV. Prevention coinfection is critical as even after HBV treatment, PLHIV with HBV coinfection experienced an increased risk of death compared to those without HBV coinfection. HBV vaccination should be scaled up among PLHIV. In addition, harm reduction prevention programs to reduce HCV infection, especially in high-risk groups, should be strengthen. For those HCV coinfected PLHIV, strategy should be explored to scale up the HCV treatment using the newer direct-acting antivirals for the whole country. The newer direct-acting antivirals have demonstrated promising results for HIV/HCV coinfected patients and have been shown to decrease mortality among PLHIV. In addition, the association between HCV and mortality was stronger in PLHIV with hyperglycemia. Hence, screening, recording and management of hyperglycemia and diabetes mellitus should be considered in this setting. Finally, testing and recording of chronic HBV and HCV status among PLHIV and monitoring the effect of HBV and HCV treatment on HIV clinical outcomes should be implemented and strengthen in HIV program.

5.3 Future directions in research

One of the major limitations of this project is using random blood glucose measurement to define hyperglycemia which has limited validity than fasting blood glucose or HbA1c measurement. In addition, there is no information on diabetes diagnosis and treatment after the random blood glucose measurement and during the follow-up. Hence, in future study, we need to measure fasting blood glucose or HbA1c to define hyperglycemia and collect information on diabetes medications. In addition, there are unmeasured confounders which we addressed using sensitivity analyses. In future study, we will collect data on cigarette smoking history which is a known risk factor for diabetes mellitus and TB disease and diabetes melilites treatment which can be associated with glycemic level and TB disease.

In this study, we only adjusted for potential confounders using the baseline patient characteristics in the final model and some covariates may have time varying effect on outcome. As this dataset has data of each visit, this could be used to analyze the time varying effect of the cofounders.

Our study cannot assess the direction of relationship between hyperglycemia and TB. Thus, future epidemiologic studies are needed to assess the direction of relationship between T2DM and TB in PLHIV using prospective longitudinal study design. In addition, longitudinal studies that assess the association between hyperglycemia with clinical outcomes such as immune restoration and mortality in HIV/TB patients are critically important to inform the clinical management. Furthermore, screening of T2DM and hyperglycemia is not integrated into most HIV care practice. Additional data is urgently needed to inform screening and clinical management of T2DM and TB comorbidity in PLHIV. Further studies that generate evidence to inform optimal timing and

methods for screening and diagnosis T2DM and management of hyperglycemia in HIV/TB patients are also needed.

In this setting, HBV and HCV infection were assessed one time at enrollment. We could not differentiate between acute, chronic or resolved coinfection and we also could not detect those who acquired coinfection during follow-up. We need to measure HBV and HCV serology panels in PLHIV longitudinally to determine the chronic infection to estimate the impact of chronic infection on T2DM and mortality.

5.4 Conclusions

Findings from this dissertation will inform clinical care of PLHIV in low- and middle-income countries. Our results suggest that 1) PLHIV with hyperglycemia and low BMI represent a subgroup with high risk of TB incidence, 2) PLHIV with active TB experience higher mortality and lower mean CD4 cell counts during the follow-up, and 3) hepatitis coinfection and hyperglycemia are associated with higher risk of mortality in PLHIV.. This dissertation also highlighted the critical need for further studies to understand the synergism between infectious and non-infectious disease comorbidities in PLHIV and the need for guidelines to prevent and manage TB, HBV, HCV and hyperglycemia in PLHIV.

Abbreviations

ART	antiretroviral therapy
CI	confidence interval
FBG	fasting blood glucose
HBV	hepatitis B virus
HbA1c	glycated hemoglobin A1c
HCV	hepatitis C virus
HIV	human immunodeficiency virus
MTB	Mycobacterium tuberculosis
PLHIV	people living with HIV
RBG	random blood glucose
T2DM	type 2 diabetes mellitus
TB	tuberculosis
WHO	World Health Organization

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