Tuberculosis Risk and Prevention: Findings from Domestic and Global Cohorts

Danae Black

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Reading Committee:

Grace John Stewart, Chair

Christine Khosropour

Sylvia Lacourse

Program Authorized to Offer Degree

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Abstract

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Danae Black

Chair of the Supervisory Committee:

Grace John Stewart, Professor

Department of Epidemiology

Tuberculosis is a highly infectious disease, leading to disproportionate morbidity and mortality amongst vulnerable populations such as immigrants, adolescents and young adults (AYA), and people living with HIV (PLWHIV). Approximately one quarter of the global population is infected with TB, which can develop into TB disease due to a myriad of factors. There has been an increasing proportion of TB cases in the U.S. attributed to non-U.S. born individuals, particularly among individuals from countries with high TB burden. Individuals who are immunocompromised, such as PLWHIV, are particularly susceptible to TB disease due to the weakened status of their immune system. Additionally heightened risk of TB during the adolescent and young adult period (age 10-24) has been linked to changes in environmental and physiological factors.

There have been changes in approaches to TB screening in the U.S; however, new screening recommendations do not account for variations of TB risk by country of origin. Additionally, gaps in

knowledge persist regarding TB risk particularly among adolescents and young adults with HIV (YWHIV). TB diagnosis is particularly difficult among children and knowledge of TB risk among YWHIV has been further hampered by dichotomized data reporting among children (less than 15) and adults (15 years of age and older). TB prevention therapy (TPT) can significantly decrease TB, especially among PLHIV on ART. TPT should be available to all PLHIV, however reporting has been prone to missingness and overlooked among YWHIV. Understanding other factors associated with TPT use and TB disease among YWHIV is of utmost importance to achieving global TB targets.

In this dissertation, we evaluate TB risk among non-U.S. born individuals, quantify TPT use among YWHIV, and evaluate TPT utilization and TB risk among YWHIV to address the current gaps in research. In Chapter 2, we estimated TB risk among non-U.S. born individuals in Washington state utilizing region of origin, World Health Organization (WHO) incidence categories, and time since entry into the U.S. In Chapters 3, we conducted the largest retrospective cohort analyses among 10,000 YWHIV in our study cohort. We estimated the TPT cascade of care, quantifying the number of YWHIV who initiated and completed TPT during our study period. We also evaluated clinic level and individuals level co-factors associated with TPT initiation and completion. Lastly in Chapter 4, we estimated the TB risk among YWHIV in Kenya and calculated TB incidence among individuals newly initated on ART and those previously on ART and evaluated co-factors for TB. Cumulatively these findings emphasize the continued need for tailored screening guidelines for non-U.S. born individuals and identified deficiencies in TPT utilization and the particularly high risk of TB among YWHIV in Kenya.

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DEDICATION

To my dad, who was my biggest champion for higher education.

David Anthony Spencer Sr.

June 18, 1958 – June 5, 2021

Chapter 1. Introduction

Background:

Domestic and global epidemiology and Tuberculosis risk among non-U.S. born individuals and adolescents and young adults with HIV

Tuberculosis (TB) is one of the deadliest infectious diseases, only recently surpassed by COVID-19 in 2020, and is the 13th leading cause of death globally.[1] TB is caused by the bacteria *Mycobacterium tuberculosis* and spreads by the exchange of aerosolized droplets. After inhaling TB droplets, an individual can be infected with the TB bacteria, however only a portion of those infected develop TB disease. TB infection or "latent" TB infection (LTBI) and is estimated to be present in approximately 1/4 of the global population. When TB infection progresses into TB disease, it occurs most commonly in the lungs and leads to symptoms such as fever, weight loss, cough and night sweats. TB disease can be particularly fatal among children under the age of 5; therefore, the Bacille Camille-Guérin (BCG) vaccine is typically provided to children at birth in countries with high TB burden to prevent the most severe forms of TB disease. Prevention of TB disease can also be achieved through the utilization of TB preventive treatment (TPT), which is recommended for people living with HIV (PLHIV), household contacts of people with TB, and other risk groups.[2]

Seventy-one percent of TB cases in the U.S. were among non-U.S. born residents in 2021.[3] Twenty-five percent of TB cases among non-U.S. born individuals were reported within the first five years of arrival.[4] Additional research among the non-U.S. born population revealed mixed results regarding the association between risk and the time to TB diagnosis following entry into the United States. In 2007 Cain et al. identified approximately one-quarter of U.S. TB cases were among non-U.S. born individuals after 5 years of residing in the United States.[5] They recommended screening non-U.S. born individuals from high-risk countries regardless of their time since U.S. entry in order to ensure adequate treatment for LTBI.[5] For example, among Filipino immigrants in California, Walter and colleagues observed a steady TB case rate over a 9 year period following entry to the U.S., highlighting the sustained risk of TB disease among this immigrant population.[6]

There is a 16-fold increased risk of active TB disease amongst PLHIV, relative to people without HIV.[7] Among the 10.6 million TB cases in 2011, 6.7% were among PLHIV. In 2021, HIV/TB co-infection was highest in the sub-Saharan Africa region. In Kenya the HIV/TB rate was 60 per 100,000 and regionally the HIV/TB rate was 42 per 100,000 persons for the Africa region. The biological mechanism for increased active TB among PLHIV is due to increased latent TB reactivation (the progression from LTBI to active TB disease) and increased susceptibility to *M. tuberculosis* infection following HIV-related immunosuppression.[8, 9] Other risk factors associated with TB disease include alcohol use, diabetes, and smoking.[10] Within the United States, there has been decreasing TB disease incidence from 1993 to 2019; however, there has been a steady increase in cases of TB disease attributable to non-U.S. born residents.[3] Hereafter, the terms 'TB cases' or 'TB incidence' refer to TB disease.

TB case notification lags among PLHIV[11] due to diversity of clinical presentation and lack of sensitive diagnostic approaches for TB diagnosis.[12] Diagnostic confirmation is a challenge among children and adolescents, particularly in resource-limited settings that utilize sputum smear microscopy as the primary diagnostic technique.[13] Sputum smear microscopy is the gold standard due to its wide spread avilability in laboratories; however, results can take multiple weeks and lack accuracy in pediatric populations.[14]

TB disease risk is also associated with age-related stressors. Adolescence, pregnancy, and older age ($\geq$ 65 years of age) are each high-risk life stages for TB reactivation and are characterized by social, emotional, and physiological changes.[14, 15] Age is associated with TB disease, with the highest risk of severe forms of TB disease among youngest children (<5 years of age), followed by a lower risk of disease among school-aged children, and thereafter a heightened risk of pulmonary TB disease during adolescence and young adulthood. There is a transition to adult-type pulmonary disease during adolescence. Adult-type pulmonary disease (primary infection, reactivation, or reinfection) includes tissue destruction and lung cavitation, the latter which promotes TB transmission.[12, 16] Tissue destruction occurs due to an excessive immune response in the immune system's attempt for disease containment. This immune mechanism is specifically observed around puberty and is hypothesized to be linked to the shift towards adult-type TB during this life phase.[17]

An estimated 1.8 million adolescents and young adults (AYA; aged 10 – 24 years of age) develop tuberculosis each year.[18] It is hypothesized that increased time spent in poorly ventilated areas[19] and extensive social networks[20] contributes AYA heightened TB risk. Increased susceptibility to TB reactivation, poor case notification, and the presence of risk factors for TB disease progression during adolescence (such as alcohol use and contracting sexually transmitted infections), cumulatively contribute to the HIV and TB risk among AYAs.[21, 22] However, age disaggregated data of TB among **adolescents and young adults with HIV (**YWHIV) are lacking.[21]

In the chapters in this dissertation, we analyzed domestic and global data to describe the TB risk among non-U.S. born individuals in WA state and TB prevention utilization and risk among YWHIV in Kenya.

Chapter 2: Tuberculosis Among Non-U.S. Born Individuals in Washington State

Without changes to current TB prevention efforts, TB elimination could be achieved among U.S. born individuals by 2100, but not among non-U.S. born individuals.[23] The elimination of federal funding for TB in 1972, simultaneous HIV epidemic, and new immigrants from countries with high TB rates led to a resurgence in TB throughout the United States.[24] In 1994, the Centers for Disease Control and Prevention (CDC) identified foreign-born persons, including children, who had arrived within 5 years from countries with high TB incidence or prevalence as a high-risk population.[25] Subsequently in 2016, the U.S. Preventive Services Task Force (USPSTF) broadened the definition of high-risk non-U.S. populations by identifying individuals born in or former residents of countries with increased TB prevalence.[26] Lastly in 2020 the CDC and USPSTF recommended LTBI testing and treatment for individuals born in or frequent travelers to countries where TB is common. These shifting recommendations highlight the increasing proportion of cases among non-U.S. born individuals from 62.6% in 2011 to 71.4% in 2021.[4]

In Chapter 2, we estimate TB risk by time since U.S. entry and World Health Organization (WHO) region of origin among non-U.S. born residents of Washington state to inform U.S. TB screening strategies.

We also estimate TB risk using WHO incidence categories to provide simplicity for clinical use when conducting TB screening among non-U.S. born individuals.

Chapter 3: Tuberculosis preventative therapy initiation and completion among adolescents and young adults with HIV in Kenya

The WHO recommended intensified case finding (ICF; TB symptom screening of high-risk populations) and the use of TB preventive therapy (TPT) among people living with HIV (PLHIV) in the absence of TB symptoms in 2011.[27] This focused application of TPT decreased TB disease by 32 percent among adults with HIV.[28] The 2020 WHO consolidated guidelines for TB further specified the inclusion of adolescents with HIV for TPT use.[2] YWHIV differ from other adolescent populations due to their regular engagement with healthcare, however their retention in care is influenced by the quality, accessibility, and provision of youth-friendly services. Disengagement from HIV care impedes TB screening and prevention opportunities for YLWH and barriers to retention include stigma, clinic factors, and fear of disclosure of HIV status.[29] TB screening and provision of TPT is a component of Kenya's Adolescent HIV care and treatment package. The Ministry of Health (MOH) recommended TPT to all PLHIV for at least 6 months in March of 2015; however due to low implementation, the MOH's 731 facility reporting tool (MOH 731) is used to report HIV indicators was revised to include indicators for TPT.[30, 31] Completion of TB intensified case finding (ICF) cards is a required aspect of monitoring and evaluation for client service provision.[32] Each month the completion of the MOH 731 form reports aggregated facility data regarding the proportion of people living with HIV (PLHIV) who are screened for TB, initiated IPT, and completed IPT.[30]

Among YLWH that initiate TPT, older AYA are less likely to complete treatment[33], in part because their parents lack understanding of the rationale for TPT.[34] Support/supervision for AYA and education for parents is necessary to ensure adherence to TPT.[33, 34] Structural and financial barriers to adherence, such as facility stock-outs and inability to afford transportation to obtain refills, also contribute to treatment non-adherence.[35, 36] Integrated HIV/TB services incentivize individuals to be adherent due to the cost of travel and time already dedicated to HIV care.[33]

In Chapter 3, we utilize programmatic data to quantify the TB prevention cascade of care, including TPT initiation and completion among HIV clinics in Kenya. We utilized a large study sample of YWHIV and multiple study sites to evaluate the individual and clinic-level factors associated with TPT initiation and completion. Our results identify gaps in TPT provision, clinic factors that influence TPT initiation and completion, and individual characteristics to focus on to improve TPT initiation and completion among YWHIV.

Chapter 4: Risk and cofactors of tuberculosis incidence among adolescents and young adults with HIV

The global TB incidence in 2021 was 134 per 100,000, with 6.7% occurring among people living with HIV.[1] The Africa region is the second highest region of TB cases, with 23% of the TB cases concentrated there.[1] TB is the leading cause of death among people with HIV and among the 703,000 PLHIV who had TB disease in 2021, only 46% were utilizing ART. ART is protective against TB, with a 2.3% reduction in TB prevalence observed among children and adolescents with HIV for every 10% increase in ART uptake.[37] Individuals newly diagnosed with HIV have a particularly elevated risk of TB, with a doubling of TB risk following HIV seroconversion.[38]

Integrated HIV/TB services are central to Kenya's progress for management of TB and HIV, including initiation on ART, TB screening, initiation of TPT, and HIV testing among TB patients.[39] However current TB outcomes among HIV patients are poor, with 3-4 times higher mortality among PLHIV and TB versus individuals diagnosed with TB without HIV.[39] There is an estimated TB incidence among PLHIV in Kenya of 60 per 100,000.[1] Additional insight into the TB risk among YWHIV is lacking due to lack of age-disaggregated reporting.

The adolescent package of care was introduced in Kenya in 2014 and aimed to provide a comprehensive guide for essential health services for adolescents, with particular emphasis on unique services for YWHIV. Alongside Kenya's National Strategic Plan for Tuberculosis, Leprosy, and Lung Health,

there is a dedication to improving adolescent health, but the needs of this group remain unclear due to lack of TPT data and age disaggregated data related to this reporting.

Chapter 4 reports TB incidence among a cohort of YWHIV on ART, stratified by newly initiating ART and previously on ART. This analysis fills a gap in adolescent health research, while also identifying potential relationships between individual characteristics and TB risk. The use of programmatic data among a sizable YWHIV cohort further emphasizes the importance of our analysis.

Summary

This dissertation evaluates TB risk among non-U.S. born individuals, accounting for their country of origin and time since U.S. entry, broadening the evidence to inform U.S. TB testing and treatment for immigrant populations. Additionally, this research strives to expand the body of research intersecting HIV, TB, and child and adolescent health by estimating TB risk and utilization of TPT among YWHIV in Kenya. Cumulatively this research highlights underserved populations that are overburdened by the TB epidemic and (1) emphasizes the importance of appropriate TB screening strategies to achieve TB elimination in the U.S.,(2) identifies gaps in integrated HIV/TB services, and (3) draws attention to the significance of reporting TB risk among age-disaggregated groups to ensure the most burdened age groups are sufficiently served.

Chapter 2: Tuberculosis Among Non-U.S. Born Individuals in Washington State

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TB risk by time since U.S. entry among non-U.S.-born residents of Washington State, USA

D. A. Black,[1] S. W. McBrien,[2] J. Gersh,[3] B. Ghassemieh,[3] M. Narita,[3,4] M. J. Pecha,[2] Y. Tan,[5] D. J. Horne[3,6]

[1]Department of Epidemiology, University of Washington, Seattle, WA, [2]Washington State Department of Health, TB Control Program, Seattle, WA, [3]Department of Medicine, University of Washington, Seattle, WA, [4]Public Health - Seattle & King County, TB Control Program, Seattle, WA, [5]Departments of Electrical & Computer Engineering, and [6]Global Health, University of Washington, Seattle, WA, USA

Correspondence to: Danae Black, Department of Epidemiology, University of Washington, Health Sciences Bldg, F-262, Box 357236, 1959 NE Pacific Street, Seattle, WA 98195, USA. email: danaesb@uw.edu

Running head: TB risk among non-U.S.-born Washington State

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SUMMARY

BACKGROUND: Progress towards TB elimination in the United States will require improved detection and treatment of latent TB infection among non-U.S.-born residents who remain at disproportionate risk of TB disease. To inform targeted testing efforts, we evaluated risk of TB disease among non-U.S.-born residents of Washington State, USA, by region of origin and time from U.S. entry.

METHODS: We conducted a retrospective cohort study among non-U.S.-born residents diagnosed with TB disease in Washington State from 2005 to 2014, for which country-specific population estimates were also available. The risk of TB disease among non-U.S.-born residents was estimated by time since U.S. entry, World Bank region of origin, and WHO TB incidence category.

RESULTS: Risk of TB disease for non-U.S.-born residents was highest within the first year after U.S. entry. Among persons from countries with high TB incidence who had resided in the United States for more than 20 years, risk for TB remained elevated.

CONCLUSION: Elevated risk of developing TB disease among individuals not born in the United States persisted long after U.S. entry, particularly among persons originating from certain regions and from high-burden countries. These findings contribute to evidence supporting a refinement of existing screening guidelines.

KEY WORDS: immigrants; epidemiology; diagnosis; infectious disease

INTRODUCTION

The U.S. goal to eliminate TB (defined as <1 case per 100,000 population) will not be achieved prior to the year 2100 at the current rate of decline.[23, 40-42] Since 2013, the majority of TB diagnoses among non-U.S.-born residents has occurred in those residing in the United States for ≥10 years.[43] The non-U.S.-born population in the United States is over 45 million, necessitating latent TB infection (LTBI) screening strategies and expanded testing and treatment of LTBI in high-risk groups,[3] including non-U.S.-born individuals.[40]

Since 2016, the U.S. Preventive Services Task Force (USPSTF) has recommended targeted LTBI testing for persons who were born in or are former residents of countries with increased TB prevalence.[44] Also, studies have demonstrated the risk for TB disease among non-U.S.-born persons may remain elevated for many years after arrival in the United States.[5] Evaluations of risk assessment tools that prioritize individuals for LTBI testing and screening have been identified as an important research gap.[44]

LTBI screening recommendations do not account for variation in TB risk by country of origin.[45] In 2019, Washington State (hereafter “Washington”) was home to more than 1 million non-U.S.-born residents (14.9% of Washington population).[46] This same year, non-U.S.-born Washington residents accounted for 77.9% of persons with TB.[47] To inform strategies for LTBI screening of non-U.S.-born Washington residents, we sought to identify risk of TB disease among non-U.S.-born Washington residents by region of origin and time since U.S. entry. We hypothesized that TB rates would remain high among non-U.S.-born residents from high TB burden regions despite long-term U.S. residence.

METHODS

Data collection

We used the Washington TB case registry to identify all persons born outside of the United States who were diagnosed with TB disease in Washington between January 1, 2005 and December 31, 2014.[48] Cohort selection included persons originating from U.S. island territories, where TB incidence is generally higher than in the United States.[49, 50]

We categorized individuals by their country of origin into one of seven regions, six regions based on the 2017 World Bank regional classification of global economies, while countries having an annual rate of TB disease <10/100,000 were assigned to a seventh category (Supplementary Table S1; hereafter "World Bank regions").[5] Categorizing these "low-incidence countries" separately minimized any downward bias within the remaining six World Bank regions. A second, separate classification of individuals was used for comparative modeling based solely on 2016 WHO TB incidence estimates by country, to create strata reflecting a more objective, homogeneous representation of TB exposure risk in native countries of origin. Class thresholds by TB incidence were defined to provide a balanced distribution of individuals across strata, with our highest incidence category following the WHO definition for high disease burden countries (>208/100,000; Supplementary Table S2).[51]

We used the American Community Survey (ACS) 2005–2009 and 2010–2014 Public Use Microdata Sample files to estimate population denominators, with sample sizes of 137,011[52] and 159,737, respectively.[53, 54] Population denominator estimates for each stratum included country-specific contributors with representation in each 5-year data set. To ensure compatibility, aggregate numerators included only those persons with TB having a country of origin represented in the denominator estimates.

Ethical approval

The Washington State Institutional Review Board, Olympia, WA, USA, approved the study.

Statistical analyses

The primary outcome of this analysis was estimated persons with TB/100,000 among non-U.S.-born Washington residents. Two independent categorical variables, based on World Bank region and estimated country of origin TB incidence, were used separately in comparative modeling. The World Bank region categorization overall provided economically similar categories to approximate TB burden. The WHO incidence categories served as a sensitivity analysis to determine if global TB rates aligned with TB rates among residents of Washington; and if so, if counterparts to these individuals could be responsible for driving the TB prevalence within World Bank Regions.

Rate of TB among non-U.S.-born residents in Washington was estimated using two Poisson regression models with robust variance estimation, including an offset to account for variations in the population denominators in 2005–2009 and 2010–2014.[55] The Poisson and negative binomial models were considered for this analysis as suitable models for count data regression. Following testing for overdispersion, there was negligible difference between the two models, and we selected the Poisson model. Descriptive and multivariate analyses were performed using RStudio v2.5001 (RStudio, PBC, Boston, MA).

RESULTS

Descriptive results

From January 1, 2005 to December 31, 2014, 2318 individuals were diagnosed with TB disease in Washington. After excluding U.S.-born individuals (*n* = 577), persons with TB counted outside of Washington (*n* = 74) and individuals diagnosed with TB prior to U.S. entry (*n* = 72), 1595 non-U.S.-born residents were included in our study. As two persons were missing country of birth and 113 originated in a country that was not included in World Bank global regions, 1480 persons with TB were included in the final analyses (Supplementary Figure S1).

The median age at time of TB diagnosis was 41.6 years (standard deviation [SD] 20.8), and 54.3% of the cohort was male (Table 1). The median age at time of U.S. entry was 28.6 years (SD 17.8) and 44.9% of the cohort had resided in the United States for ≥10 years at the time of their TB diagnosis. Almost half (46.8%) of the cohort was from the East Asia and Pacific (EAP) Region, 19.3% from Latin America, South America, and the Caribbean (LSAC), and 18.1% from sub-Saharan Africa (SSA) (Table 1). The time between U.S. entry and TB diagnosis varied widely across regions, being approximately 9 years among individuals from LSAC, while greater than 50 years among individuals from low-incidence countries. The median age at TB diagnosis also varied notably across regions, from 30.9 among individuals from SSA to 78.2 among those from low-incidence countries. The five countries with the highest number of non-U.S.-born persons with TB were the Philippines (17.0%), Mexico (14.7%), Vietnam (14.0%), India (8.1%), and Ethiopia (7.9%; Table 2). A total of 42.1% of individuals emigrated from the highest incidence category of ≥208/100,000 persons (Table 3).

Poisson regression models

Poisson regression was used to model TB rates after U.S. entry. Supplementary Tables S1 and S2 show the rates of TB disease by time in the United States categorized by World Bank region and TB incidence in the country of origin. For all groups, TB rates were highest in the first year after U.S. entry and decreased over time in the United States (Figure 1). We observed that TB rates among individuals from SSA, EAP, and South Asian regions remained >10/100,000 for at least 10 years after U.S. entry. For individuals from SSA, TB incidence remained >20/100,000 for all categories of time since U.S. entry (Figure 1).

When modeled by TB incidence in the country of origin, incidence after U.S. entry was different for those from countries with TB incidence <101/100,000 compared to ≥101/100,000 (Figure 2; Supplementary Table S2). For the former group, TB incidence 1–5 years after U.S. entry was <10/100,000, and <5/100,000 persons ≥5 years after U.S. entry. For individuals from countries with TB incidence of >101/100,000 persons, incidence remained >20/100,000 for the first 10 years after U.S. entry and remained >10/100,000 persons for all categories of time in the United States.

DISCUSSION

Our goal in the current study was to develop estimates of TB risk to inform LTBI screening strategies among non-U.S.-born individuals who reside in Washington, particularly long-term residents. We found that risk for TB disease is more dependent on region of origin than time since U.S. entry. Although TB incidence declined over time in the United States for all countries of origin, individuals from high-burden countries (>101/100,000) or from SSA, EAP, and South Asia, remain at elevated TB risk for ≥10 years after U.S. entry. The 2012 U.S. guidelines recommended targeted testing and treatment of LTBI among non-U.S.-born residents who have been in the United States 5 years or less.[56] For a given region of origin, the risk for TB is highest within 1 year after entry, likely reflecting individuals with TB disease or incipient TB at the time of U.S. entry.[57] However, for individuals from high TB burden regions, the risk for TB more than 20 years after U.S. entry approaches the risk of newly arrived individuals from lower TB burden regions. The 1999 guidelines from the U.S. Centers for Disease Control and Prevention (CDC) recommended targeted testing and treatment of LTBI among non-U.S.-born individuals who have been in the United States 5 years or less.[56, 58] Although these guidelines have not been updated in the interim, the USPSTF issued a

recommendation in 2016 that individuals from countries with increased TB risk undergo LTBI screening without addressing length of time since U.S. entry.[44]

Prior studies of TB among non-U.S.-born individuals identified heightened TB risk even after 5 years of U.S. residency.[5, 6] These studies limited evaluations to specific countries or aggregated all non-U.S.-born individuals together when evaluating the impact of time since U.S. entry. A recently published study found that the WHO TB rate by country did not consistently agree with the rate among U.S. residents from that country,[59] potentially due to differences between individuals who emigrate compared to those who stay, the effects of re-infection in high-burden settings, or other causes. Our finding that TB rates in individuals from countries with an incidence of 101–208/100,000 was higher than those from countries with a rate >208/100,000 in the first year after U.S. entry may be due to differences between individuals who emigrate compared to overall rates in the country of origin. Generally, the TB rates reported in the study by Tsang et al. were slightly higher than our estimates, although time since U.S. entry >10 years was considered as a single interval.[59]

Strengths of the present study include evaluations by region of origin and TB incidence in the countries of origin, and the use of relatively narrow intervals since time from U.S. entry. Because we evaluated TB diagnoses after U.S. entry, our estimates of TB rates include progression from infection that was acquired prior to U.S. arrival and exposures that may have occurred post-arrival.[60] Our use of state data offers an approach for other states to use TB surveillance data and publicly available ACS information to model TB risk among non-U.S.-born individuals at the state level. Prior studies of TB among non-U.S.-born residents identified heightened TB risk even after 5 years of U.S. residency.[44, 59] These studies limited evaluations to specific countries or aggregated all non-U.S.-born residents together when evaluating the impact of time since U.S. entry. Strengths of the present study include evaluations by region of origin and TB incidence in the countries of origin, and the use of relatively narrow intervals since time from U.S. entry.

Approximately 44 million persons U.S. residents (13.5% of the U.S. population are non-U.S.-born precluding the performance of LTBI screening in the entire sub-population.[61] Different strategies that have been advocated to screen the non-U.S.-born population include a simplified strategy that encourages LTBI screening in any non-U.S.-born resident (unless from a low-incidence country) regardless of the patient's time since U.S. entry or current age,[61, 62] versus risk-based targeting of non-U.S.-born residents that is not

based on time since U.S. entry.[63] An advantage of the former strategy is ease of use by busy clinicians, whereas the latter strategy leads to a more efficient use of resources. The use of a single category of non-U.S.-born population when determining risk for TB has been criticized as grouping together individuals with widely varying risks based on country of origin and time since U.S. entry.[45] Using readily available data on TB incidence rates by country or region of birth, time since U.S. entry, and individual age, we suggest that LTBI screening recommendations could be developed to recommend screening if the estimated rate exceeds a specified threshold. Based on our study results and establishing a (non-evidence based) cut-off TB prevalence of 10/100,000 persons, potential screening recommendations in Washington State could include all non-U.S.-born individuals from countries with increased TB prevalence who arrived within the prior 5 years, except for those from Asia (capturing those from East Asia and the Pacific, and South Asia) with a cut-off of 10 years and individuals from SSA with a cut-off of 20 years. As Mexico accounts for the second largest source of TB in Washington, Mexican-born individuals could be screened for a longer period of time after arrival (e.g., 10 years). A recent study that evaluated TB among all non-U.S.-born individuals in 2000–2016 identified a cohort effect among individuals from the same country of effect, reflecting differing rates of LTBI by birth year.[64] This suggests that LTBI screening recommendations should be based on recent and granular data to inform the most effective screening strategies.

The ethics of TB elimination has been questioned based on the need to offer LTBI screening and treatment to individuals who are more likely to be harmed than benefit.[63, 65] This is an important point, and could be addressed, in part, by targeting interventions toward individuals with higher risk of LTBI progression. For non-U.S.-born residents, country of origin and time in the United States should inform LTBI screening and treatment recommendations.

Our study had several limitations. The period included a change in pre-immigration screening practices. In 2007, the CDC issued new instructions on overseas screening to perform culture in individuals with abnormal chest radiographs, and this change was associated with a decline in persons with TB among non-U.S.-born residents.[66, 67] However, the impact of this change on our study results is likely to be low, as culture-based screening recommendations were implemented early in our study period, and this change was unlikely to have much impact on our TB incidence estimates for individuals >1 year after U.S. entry. Second, we excluded persons with TB from 17 countries of origin due to unavailable population data.

Specifically, the population data from ACS were aggregated into regions that did not align with the TB prevalence data from the Washington Department of Health. Exclusion of these persons and non-specific population data led to a conservative estimate of TB rates, which otherwise would result in an overestimate due to inclusion of persons with TB without representative population data. In certain circumstances, it will be found that the observed variance is greater than the mean when using the Poisson model, which is known as overdispersion. We assessed additional model types (Poisson vs. negative binomial) to minimize overdispersion and standard errors; however, similar unexplained trends were observed in a plotted hanging rootogram and the interpretation of the model estimates was similar due to the small amount of overdispersion. Third, in our modeling we were unable to account for time residing outside the United States after the initial entry date, an opportunity to acquire re-infection with *M. tuberculosis*, a risk factor for TB progression that would be loosely related to time since U.S. entry.

In conclusion, we have found that non-U.S.-born residents from high-burden countries or the World Bank regions of SSA, EAP, and South Asia are at greatly increased risk of TB for at least 10 years after U.S. entry. A strategy that treats all non-U.S.-born residents as being in the same TB risk category will result in overtreatment of many and under treatment of some, due to inefficient targeting of resources. We offer a method to focus state-wide priorities, using locally collected epidemiologic data to identify high-risk non-U.S.-born residents.

Table 1. Individual characteristics of persons with TB reported among non-U.S.-born residents of Washington State, 2005–2014, by World Bank Region*

	East Asia and Pacific *n* (%)	Eastern Europe and Central Asia *n* (%)	Latin America, South America, and the Caribbean *n* (%)	Low-incidence countries *n* (%)	Middle East and North Africa *n* (%)	South Asia *n* (%)	Sub-Saharan Africa *n* (%)	All individuals *n* (%)
Patient	692 (46.8)	65(4.4)	285(19.3)	21(1.4)	7(0.5)	142(9.6)	268(18.1)	1480(100.0)
Age at first evidence of TB disease, years, median (SD)	51.6 (20.1)	46.0 (27.2)	37.9 (17.5)	78.2 (20.6)	72.2 (28.5)	33.6 (21.4)	30.9 (16.6)	41.6 (20.8)
Age at U.S. entry, years, median (SD)	33.2 (17.7)	37.0 (25.4)	23.5 (14.9)	24.0 (14.5)	56.2 (24.7)	27.1 (19.2)	25.4 (15.7)	28.6 (17.8)
Sex								
Male	375 (54.2)	28 (43.1)	181 (63.5)	7 (33.3)	2 (28.6)	78 (54.9)	132 (49.3)	803 (54.3)
Female	317 (45.8)	37 (56.9)	104 (36.5)	14 (66.7)	5 (71.4)	64 (45.1)	136 (50.7)	677 (45.7)
HIV-positive	9 (1.3)	0 (0.0)	18 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	22 (8.2)	49 (3.3)
Diabetes	107 (15.5)	3 (4.6)	29 (10.2)	2 (9.5)	0 (0.0)	14 (9.9)	14 (5.2)	169 (11.4)
Homeless within 1 year of TB diagnosis	7 (1.0)	0 (0.0)	32 (11.2)	1 (4.8)	0 (0.0)	1 (0.7)	8 (3.0)	49 (3.3)
Time from U.S. entry to diagnosis, years, median (SD)	12.8 (12.1)	9.0 (9.6)	7.8 (12.)	50.2 (19.9)	16.7 (10.)	5.5 (8.9)	3.5 (6.7)	8.26 (12.2)
Time since U.S. entry, years								
<1	89 (12.9)	13 (20.0)	37 (13.0)	0 (0.0)	1 (14.3)	27 (19.0)	60 (22.4)	227 (15.3)
1–<5	104 (15.0)	9 (13.8)	66 (23.2)	1 (4.8)	1 (14.3)	40 (28.2)	108 (40.3)	329 (22.2)
5–<10	99 (14.3)	15 (23.1)	62 (21.8)	0 (0.0)	0 (0.0)	31 (21.8)	53 (19.8)	260 (17.6)
10–<20	179 (25.9)	23 (35.4)	48 (16.8)	1 (4.8)	3 (42.9)	23 (16.2)	35 (13.1)	312 (21.1)
>20	221 (31.9)	5 (7.7)	72 (25.3)	19 (90.5)	2 (28.6)	21 (14.8)	12 (4.5)	352 (23.8)

* World Bank Region categorized by their country of origin as “low-incidence” category (<10/100,000) or to one of six World Bank regions based on the 2017 World Bank regional classification of global economies.

SD = standard deviation.

Table 2. Number of persons with TB among non-U.S.-born residents of Washington State, USA, 2005–2014, by top 15 countries*

Country*	World Bank Region	WHO incidence category per 100,000	*n* (%)
Philippines	East Asia and Pacific	≥208	252 (17.0)
Mexico	Latin America, South America, and the Caribbean	10–49.9	217 (14.7)
Vietnam	East Asia and Pacific	101–207.9	207 (14.0)
India	South Asia	≥208	120 (8.1)
Ethiopia	sub-Saharan Africa	101–207.9	117 (7.9)
Somalia	sub-Saharan Africa	≥208	92 (6.2)
Cambodia	East Asia and Pacific	≥208	63 (4.3)
China	East Asia and Pacific	50–100.9	61 (4.1)
Kenya	sub-Saharan Africa	≥208	34 (2.3)
Ukraine	Eastern Europe and Central Asia	50–100.9	27 (1.8)
Burma	East Asia and Pacific	≥208	26 (1.8)
Guatemala	Latin America, South America, and the Caribbean	10–49.9	24 (1.6)
Laos	East Asia and Pacific	101–207.9	21 (1.4)
Indonesia	East Asia and Pacific	≥208	14 (0.9)
Russia	Eastern Europe and Central Asia	50–100.9	12 (0.8)
Federated States of Micronesia	East Asia and Pacific	101–207.9	

*The top 15 countries (*n* = 1287) represent 87.0% of the total persons with TB in Washington State, USA, 2005–2014.

Table 3. Individual characteristics of non-U.S.-born residents with TB, Washington State, USA, 2005–2014, by country incidence category

	<10/100,000 *n* (%)	10–49.9/100,000 *n* (%)	50–100.9/100,000 *n* (%)	101–207.9/100,000 *n* (%)	≥208/100,000 *n* (%)	Total *n* (%)
Patients	21 (1.4)	279 (18.9)	152 (10.3)	405 (27.4)	623 (42.1)	1480
Age at first evidence of active TB, years, median (SD)	72.0 (19.7)	39.4 (18.9)	57.3 (24.6)	37.2 (19.5)	42.4 (20.5)	41.6 (20.8)
Age of U.S. entry, years, median (SD)	22.6 (19.9)	24.5 (15.7)	39.2 (21.2)	27.7 (17.1)	29.9 (17.5)	28.6 (17.8)
Sex						
Male	12 (57.1)	172 (61.6)	84 (55.3)	208 (51.4)	327 (52.5)	803 (54.3)
Female	9 (42.9)	107 (38.4)	68 (44.7)	197 (48.6)	296 (47.5)	677 (45.7)
HIV-positive	1 (4.8)	16 (5.7)	0 (0.)	18 (4.4)	14 (2.2)	49 (3.3)
Diabetes	2 (9.5)	31 (11.1)	13 (8.6)	37 (9.1)	86 (13.8)	169 (11.4)
Homeless	2 (9.5)	30 (10.8)	2 (1.3)	9 (2.2)	6 (1.0)	49 (3.3)
Time from U.S. entry to diagnosis, years, median (SD)	45.9 (24.3)	8.71 (12.8)	10.1 (11.7)	8.09 (9.6)	7.17 (11.9)	8.26 (12.2)
Time since U.S. entry, years						
<1	1 (4.8)	29 (10.4)	25 (16.4)	62 (15.3)	110 (17.7)	227 (15.3)
1–<5	1 (4.8)	63 (22.6)	24 (15.8)	94 (23.2)	147 (23.6)	329 (22.2)
5–<10	1 (4.8)	61 (21.9)	27 (17.8)	70 (17.3)	101 (16.2)	260 (17.6)
10–<20	1 (4.8)	51 (18.3)	46 (30.3)	102 (25.2)	112 (18.)	312 (21.1)
>20	17 (81.0)	75 (26.9)	30 (19.7)	77 (19.0)	153 (24.6)	352 (23.8)

SD = standard deviation.

Figure 1. Poisson model estimates of non-U.S.-born Washington State residents with TB per 100,000 by World Bank Region and time since U.S. entry, 2005–2014. TB rates were highest in the first year after U.S. entry and decreased over time in the United States. TB rates remained elevated (>10/100,000) for at least 10 years after U.S. entry among individuals from SSA, EAP, and South Asian regions.

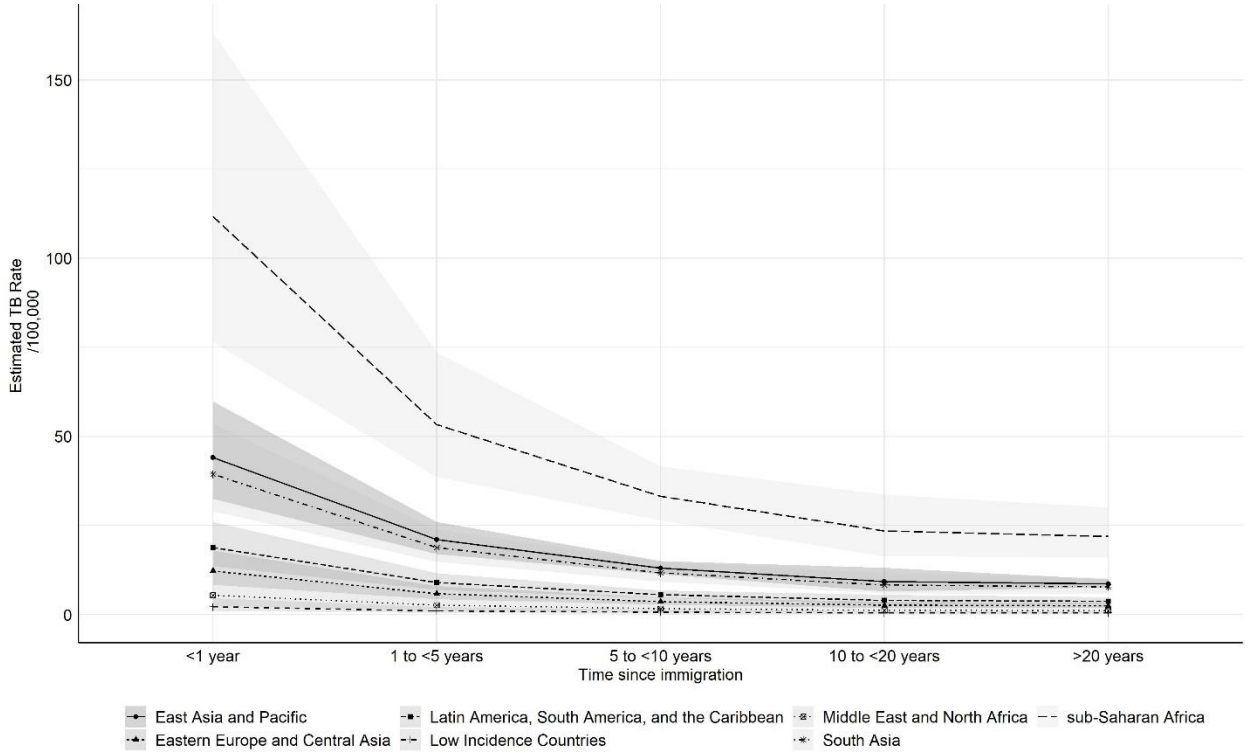
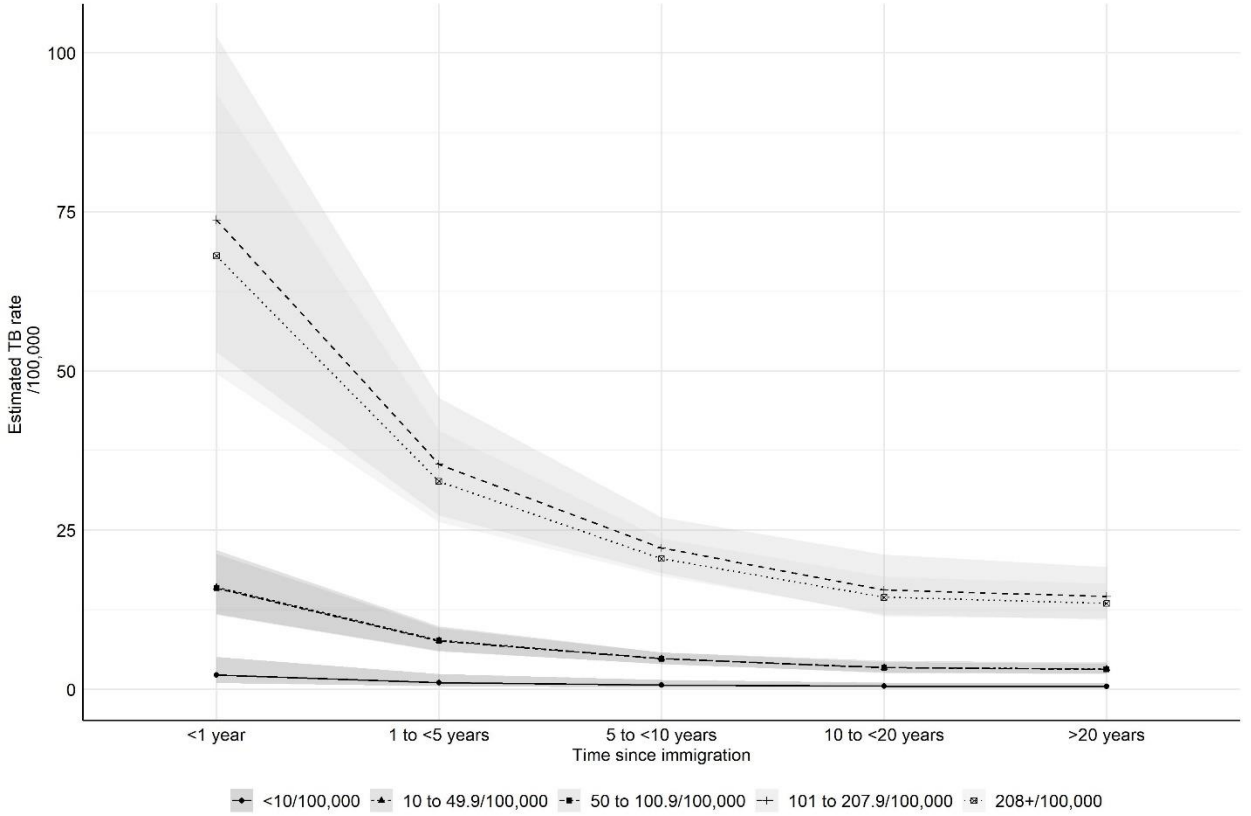


Figure 2 Poisson model estimates of non-U.S.-born Washington State residents with TB per 100,000 by WHO TB incidence and time since U.S. entry, 2005–2014. Overall, TB incidence after U.S. entry varied among those from countries in <101/100,00 compared to ≥101/100,000 TB incidence categories. For individuals from countries with TB incidence of >101/100,000 persons, TB incidence remained >10/100,000 persons for all categories of time in the United States. Note: The values of TB prevalence among the 10–49.9 and 50–100.9/100,000 were very similar and the lines are overlapping.



SUPPLEMENTARY DATA

WA STATE DATA

Verification as a Report of Verified Case of Tuberculosis (RVCT) was confirmed against diagnostic data existing in the case record. Date of diagnosis was assigned as the earliest collection among positive clinical specimen(s) used to support the case's confirmed verification status, or date of initial report if verified by provider diagnosis. This study was approved by the Washington State Institutional Review Board.

The calendar date of U.S. entry was set by tuberculosis (TB) registry default as the first day of the month and year as recorded in the RVCT case record. Age at U.S. entry was calculated in years from date of birth to date of entry. Time from U.S. entry to TB diagnosis was calculated in years from date of entry to date of diagnosis. Case records were included if individuals were counted as a TB case by Washington State and were diagnosed with TB after U.S. entry. Cases were excluded from the study if their country of birth was missing or not specified.

The Electronic Disease Notification (EDN) system is administrated by the Centers for Disease Control and Prevention and used to collect and communicate data related to demographics, overseas medical examination and treatment, as well as follow-up after U.S. entry on all foreign nationals entering under an immigrant or refugee visa. For matched cases EDN was the principal source of data on date of entry to the U.S. and diagnostic class assigned to the immigrant's TB condition at the time of overseas medical examination.

Our use of state data offers an approach for other states to use TB surveillance data and publicly available ACS information to model TB risk among non-U.S.-born individuals at the state level.

STRATIFICATION

Strata by incidence were defined by parsing the World Health Organization (WHO) global distribution of country-specific TB estimates proportionally), using the WHO threshold for high-burden countries as the final boundary. Certain countries dominate the regional or WHO categories, which the authors recognize as a limitation of state-level data, due to differing immigration patterns by state and lack of generalizability

to other states. Conversely an advantage of this approach provides a blueprint for other states to replicate this analysis to develop recommendations related to state-specific immigration patterns.

PUBLIC USE MICRODATA SAMPLE (PUMS) DATA

The data sets include country of birth and year of entry to the United States.17,19 Countries were excluded from population denominator estimates (stratified by country of origin or TB incidence categories) if data were not available for both 5-year data sets, or if a corresponding place of birth code (POBP) represented multiple countries (i.e. “Northern Africa, not specified”). Countries excluded from the American Community Survey (ACS) population denominator estimates were similarly excluded from the cohort. The TB case counts were aggregated by country and year.

STATISTICAL ANALYSES

The offset also allows the model coefficient estimates to be reported as a rate, as opposed to reporting the relative risk. The outcome variable of TB case counts is regressed on the predictors of time since entry to the U.S. and modified World Bank region indicators in the first model. In the second model, the outcome variable of TB case counts is regressed on the predictors of time since entry to the U.S. and TB incidence categories.

Table S1. Country classification by World Bank region

Country	World Bank Region
AMERICAN SAMOA	East Asia and Pacific
BURMA	East Asia and Pacific
CAMBODIA	East Asia and Pacific
CHINA	East Asia and Pacific
FED STATES MICRONESIA	East Asia and Pacific
FIJI	East Asia and Pacific
GUAM	East Asia and Pacific
HONG KONG	East Asia and Pacific
INDONESIA	East Asia and Pacific
LAOS	East Asia and Pacific
MALAYSIA	East Asia and Pacific
PHILIPPINES	East Asia and Pacific
TAIWAN	East Asia and Pacific
THAILAND	East Asia and Pacific
TONGA	East Asia and Pacific
VIETNAM	East Asia and Pacific
WESTERN SAMOA	East Asia and Pacific
AZERBAIJAN	Eastern Europe and Central Asia
BOSNIA AND HERZEGOVINA	Eastern Europe and Central Asia
BULGARIA	Eastern Europe and Central Asia
GEORGIA	Eastern Europe and Central Asia
KAZAKHSTAN	Eastern Europe and Central Asia
LATVIA	Eastern Europe and Central Asia
MOLDOVA	Eastern Europe and Central Asia
ROMANIA	Eastern Europe and Central Asia
RUSSIA	Eastern Europe and Central Asia
UKRAINE	Eastern Europe and Central Asia
UZBEKISTAN	Eastern Europe and Central Asia
YUGOSLAVIA	Eastern Europe and Central Asia
BOLIVIA	Latin America, South America, and the Caribbean
BRAZIL	Latin America, South America, and the Caribbean
CHILE	Latin America, South America, and the Caribbean
CUBA	Latin America, South America, and the Caribbean
DOMINICAN REPUBLIC	Latin America, South America, and the Caribbean
ECUADOR	Latin America, South America, and the Caribbean
EL SALVADOR	Latin America, South America, and the Caribbean
GUATEMALA	Latin America, South America, and the Caribbean

GUYANA	Latin America, South America, and the Caribbean
HAITI	Latin America, South America, and the Caribbean
HONDURAS	Latin America, South America, and the Caribbean
MEXICO	Latin America, South America, and the Caribbean
NICARAGUA	Latin America, South America, and the Caribbean
PARAGUAY	Latin America, South America, and the Caribbean
PERU	Latin America, South America, and the Caribbean
PUERTO RICO	Latin America, South America, and the Caribbean
VENEZUELA	Latin America, South America, and the Caribbean
ALGERIA	Middle East and North Africa
IRAN	Middle East and North Africa
MOROCCO	Middle East and North Africa
YEMEN	Middle East and North Africa
AFGHANISTAN	South Asia
BANGLADESH	South Asia
INDIA	South Asia
NEPAL	South Asia
PAKISTAN	South Asia
CAMEROON	sub-Saharan Africa
ERITREA	sub-Saharan Africa
ETHIOPIA	sub-Saharan Africa
KENYA	sub-Saharan Africa
LIBERIA	sub-Saharan Africa
NIGERIA	sub-Saharan Africa
SIERRA LEONE	sub-Saharan Africa
SOMALIA	sub-Saharan Africa
SUDAN	sub-Saharan Africa
TANZANIA UNITED REP OF	sub-Saharan Africa
UGANDA	sub-Saharan Africa
ZIMBABWE	sub-Saharan Africa
CANADA	Low Incidence Countries
DENMARK	Low Incidence Countries
FRANCE	Low Incidence Countries
GERMANY	Low Incidence Countries
IRELAND	Low Incidence Countries
ITALY	Low Incidence Countries
JAPAN	Low Incidence Countries
SPAIN	Low Incidence Countries
SWITZERLAND	Low Incidence Countries

UNITED KINGDOM	Low Incidence Countries

Table S2. Country classification by WHO incidence category

Country	**TB Incidence Category**
AMERICAN SAMOA	<10/per 100k
CANADA	<10/per 100k
CUBA	<10/per 100k
DENMARK	<10/per 100k
FRANCE	<10/per 100k
GERMANY	<10/per 100k
IRELAND	<10/per 100k
ITALY	<10/per 100k
PUERTO RICO	<10/per 100k
SWITZERLAND	<10/per 100k
TONGA	<10/per 100k
UNITED KINGDOM	<10/per 100k
WESTERN SAMOA	<10/per 100k
BOSNIA AND HERZEGOVINA	10-49.9/per 100k
BRAZIL	10-49.9/per 100k
BULGARIA	10-49.9/per 100k
CHILE	10-49.9/per 100k
GUATEMALA	10-49.9/per 100k
HONDURAS	10-49.9/per 100k
IRAN	10-49.9/per 100k
JAPAN	10-49.9/per 100k
LATVIA	10-49.9/per 100k
MEXICO	10-49.9/per 100k
NICARAGUA	10-49.9/per 100k
PARAGUAY	10-49.9/per 100k
SPAIN	10-49.9/per 100k
VENEZUELA	10-49.9/per 100k
YEMEN	10-49.9/per 100k
YUGOSLAVIA	10-49.9/per 100k
ALGERIA	50-100.9/per 100k
AZERBAIJAN	50-100.9/per 100k
CHINA	50-100.9/per 100k
DOMINICAN REPUBLIC	50-100.9/per 100k
ECUADOR	50-100.9/per 100k

EL SALVADOR	50-100.9/per 100k
ERITREA	50-100.9/per 100k
FIJI	50-100.9/per 100k
GEORGIA	50-100.9/per 100k
GUAM	50-100.9/per 100k
GUYANA	50-100.9/per 100k
HONG KONG	50-100.9/per 100k
KAZAKHSTAN	50-100.9/per 100k
MALAYSIA	50-100.9/per 100k
ROMANIA	50-100.9/per 100k
RUSSIA	50-100.9/per 100k
TAIWAN	50-100.9/per 100k
UKRAINE	50-100.9/per 100k
UZBEKISTAN	50-100.9/per 100k
AFGHANISTAN	101-207.9/per 100k
BOLIVIA	101-207.9/per 100k
CAMEROON	101-207.9/per 100k
ETHIOPIA	101-207.9/per 100k
FED STATES MICRONESIA	101-207.9/per 100k
HAITI	101-207.9/per 100k
LAOS	101-207.9/per 100k
MOLDOVA	101-207.9/per 100k
MOROCCO	101-207.9/per 100k
NEPAL	101-207.9/per 100k
PERU	101-207.9/per 100k
SUDAN	101-207.9/per 100k
THAILAND	101-207.9/per 100k
UGANDA	101-207.9/per 100k
VIETNAM	101-207.9/per 100k
BANGLADESH	208+/per 100k
BURMA	208+/per 100k
CAMBODIA	208+/per 100k
INDIA	208+/per 100k
INDONESIA	208+/per 100k
KENYA	208+/per 100k
LIBERIA	208+/per 100k
NIGERIA	208+/per 100k
PAKISTAN	208+/per 100k
PHILIPPINES	208+/per 100k

SIERRA LEONE	208+/per 100k
SOMALIA	208+/per 100k
TANZANIA UNITED REP OF	208+/per 100k
ZIMBABWE	208+/per 100k

Table S3. Multivariate model estimates of TB Rates, by Modified World Bank Region and Time since United States Entry

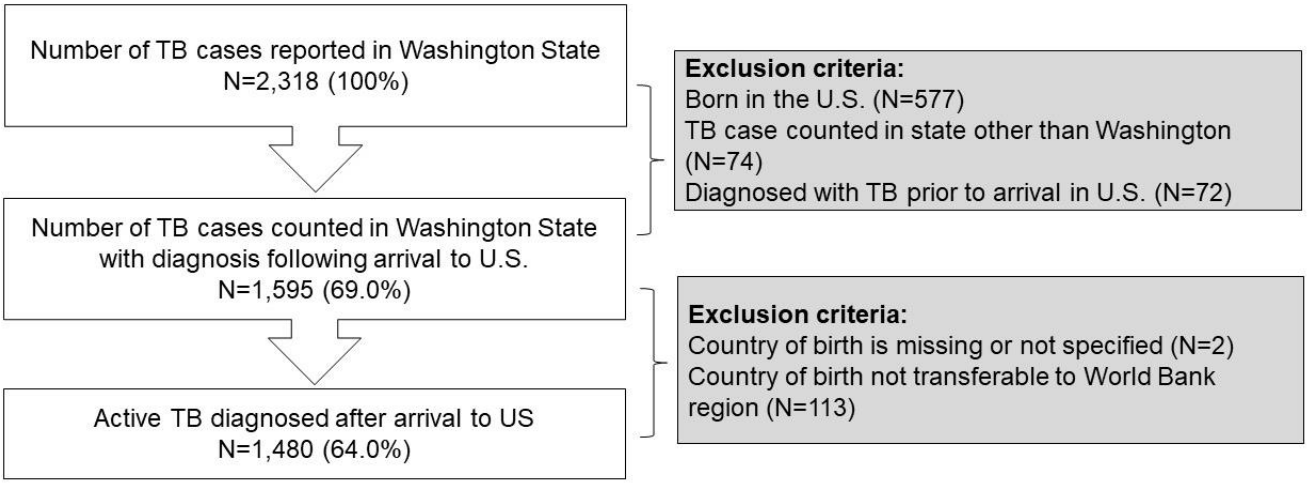
Time since U.S. Entry	East Asia and Pacific	Eastern Europe and Central Asia	Latin America, South America, and the Caribbean	Low Incidence Countries	Middle East and North Africa	South Asia	sub-Saharan Africa
<1 year	44.05	12.23	18.79	2.15	5.41	39.38	111.71
1 to <5 years	21.01	5.84	8.96	1.02	2.58	18.78	53.29
5 to < 10 years	13.08	3.63	5.58	0.64	1.61	11.69	33.16
10 to <20 years	9.24	2.57	3.94	0.45	1.14	8.26	23.44
>20 years	8.67	2.41	3.70	0.42	1.06	7.75	21.99

Table S4. Multivariate model estimates of TB Rates, by WHO Incidence and Time since United States Entry

Time since U.S. Entry	<10/per 100k	10-49.9/per 100k	50-100.9/per 100k	101-207.9/per 100k	208+/per 100k
<1 year	2.23	16.02	15.86	73.75	68.13
1 to <5 years	1.07	7.68	7.61	35.36	32.67
5 to < 10 years	0.67	4.82	4.78	22.21	20.52
10 to <20 years	0.47	3.39	3.36	15.62	14.44
>20 years	0.44	3.17	3.13	14.57	13.47

Figure S1. Population selection

Population selection. Details inclusion and exclusion criteria for selection of TB cases selected for analysis.



Chapter 3: Tuberculosis preventative therapy initiation and completion among adolescents and young adults with HIV in Kenya

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Tuberculosis preventative therapy initiation and completion among adolescents and young adults with HIV in Kenya

Danae A Black, MPH[a], Sylvia M. LaCourse, MPH, MD[a,b,c], Irene N Njuguna, MBChB, MSc, PhD [c,d], Kristin M Beima-Sofie, MPH, PhD[c], Caren W Mburu, MBChB, MMeD[e], Cyrus Mugo, MBChB, MPH[c,d], Janet A Y Itindi[f], Alvin D Onyango[e], Barbra A Richardson, PhD[c,g], Dalton C Wamalwa, MBChB, MMed, MPH[e], Grace C John-Stewart, MPH, MD, PhD[a, b, c, h]

[a] Department of Epidemiology, University of Washington, Seattle, Washington, USA

[b] Department of Medicine, University of Washington, Seattle, Washington, USA

[c] Department of Global Health, University of Washington, Seattle, Washington, USA

[d] Kenyatta National Hospital, Nairobi, Kenya

[e] Department of Pediatrics and Child Health, University of Nairobi, Nairobi, Kenya

[f] Kenya Medical Research Institute, Nairobi, Kenya

[g] Department of Biostatistics, University of Washington, Seattle, Washington, USA

[h] Department of Pediatrics, University of Washington, Seattle, Washington, USA

Corresponding Author: Danae Black, Department of Epidemiology, University of Washington, UW Box #351619, Seattle, WA 98195, danaesb@uw.edu

Running head: TB prevention for Kenyan young people with HIV

Background

Tuberculosis (TB) is the leading cause of death among adolescents and young adults with HIV (YWHIV). and their heightened risk warrants deeper understanding of utilization of TB-prevention measures within HIV care.

Setting

Retrospective study using clinic surveys and medical record data from 86 Kenyan HIV clinics.

Methods

Clinic surveys obtained information on TPT services. Medical records of YWHIV were abstracted. Bivariate and multivariate analyses used generalized linear models to determine individual- and clinic-level cofactors of TPT initiation and completion.

Results

Among 10,328 eligible YWHIV, 4337 (42.0%) initiated TPT. Of 3295 with >6 months follow-up, 1774 (53.8%) completed TPT. Lower patient-to-staff ratio was a clinic-level cofactor of TPT initiation (p=0.044) and completion (p=0.004); designated adolescent areas were associated with TPT initiation (prevalence ratio (PR) 2.05 [95% CI:1.46-2.88]). Individual cofactors of TPT initiation included younger age at HIV-care enrollment (relative risk (RR) 0.85[95% CI:0.80-0.90]) and ART duration (1-2 vs. <1 year RR 1.31[95% CI:1.18-1.45]. TPT completion was associated with younger age (RR 0.91[95% CI:0.85-0.98]) and ART duration (2–5 vs. <1 year RR 1.27[95% CI:1.03-1.57]. In multivariate models, TPT initiation was associated with younger age and ART duration (1-2 vs. 1 year; adjusted RR (aRR) 1.30[95% CI:1.16-1.46]), and TPT completion with ART duration (2-5 vs. 1 year aRR 1.23[95% CI:0.99-1.52]).

Conclusion

Over half of YWHIV did not initiate and >40% did not complete TPT, with distinct clinic-level and individual-level cofactors. Approaches to enhance adolescent-friendly infrastructure and support older YWHIV are necessary to improve TPT use.

Key Words: Tuberculosis; Prevention; Adolescent; HIV; care cascade

INTRODUCTION

Tuberculosis (TB) is a leading cause of death among adolescents and young adults living with HIV (YWHIV), who are at high risk of TB infection and disease.[21, 68] Young people (10 to 24 years of age) make up nearly a quarter of the global population and require specialized attention to meet their health needs.[69] With 90% of global YWHIV residing in sub-Saharan Africa (SSA), there is a need for treatment approaches tailored to this group.[21] Tuberculosis preventive therapy (TPT) in combination with antiretroviral therapy (ART) significantly reduces the risk of TB and mortality.[70] Since 2011, the World Health Organization (WHO) recommends TPT for YWHIV as part of routine HIV care.[2]

Globally, only 29% of the five-year target total TPT for 2018-2022 was distributed as of 2020.[71] More than 80% of TPT was distributed to PLHIV, though global estimates specifically among YWHIV are lacking.[71] Monitoring initiation and completion of TPT are among core national HIV indicators recommended in the 2020 WHO consolidated guidance for TB.[2] In a study among PLHIV on ART in Kenya, 69% initiated and 95% completed TPT; however, only 11% of individuals were ages 10-24 and routine TB screening was lowest among those aged 20-24 when compared to other age groups.[72] Studies among children and adults cite healthcare worker (HCW) knowledge gaps, lack of adequate health system infrastructure, and misconceptions associated with preventive treatment as barriers for TPT, however these difficulties are not well understood for YWHIV.[73]

Understanding individual- and clinic-level factors associated with TPT initiation and completion in YWHIV is necessary to optimize TB prevention efforts for this high-risk population. We conducted a nested study within a cohort of >15,000 YWHIV from 101 comprehensive HIV care clinics (CCCs) throughout Kenya.[74] We analyzed 2 years of programmatic medical record data to evaluate the TB prevention cascade and investigated individual and clinic-level characteristics associated with TPT initiation and completion.

METHODS

Kenya's TPT rollout for PLHIV started in 2015, with expanded implementation in 2016.[72] Kenyan guidelines recommend PLHIV should be screened for TB symptoms at each clinical visit (intensified case finding (ICF))

and, upon exclusion of TB, TPT should be offered to all PLHIV >12 months of age and recorded on the ICF/isoniazid preventive therapy (IPT) card.[75, 76] TPT is dispensed at CCC pharmacies, primarily during routine visits.[77] In 2020, an estimated 78% of PLHIV newly enrolled in HIV care in Kenya received TPT, but estimates by age are unknown.[71]

We utilized data from the Adolescent Transition to Adult Care for HIV-infected Adolescents in Kenya study [NCT03574129], which developed and evaluated an adolescent transition package to support independence among YWHIV in HIV care. A previous publication provided a detailed study description.[74] This study was approved by the University of Washington Institutional Review Board (IRB) and Kenyatta National Hospital/University of Nairobi Ethical Review Committee (ERC). Additional approval was obtained from Kenya's National AIDS and STI Control Program, County Departments of Health, and managers of the participating clinics. Both the IRB and the ERC waived the requirement for consent.

Patient medical records for YWHIV aged 10-24 were manually abstracted by a mobile data team for the 2-year period from January 1, 2016, to December 31, 2017 (hereafter referred to as the study period), and the earliest date of data abstraction was January 8, 2018. Abstracted variables included demographics, HIV WHO stage, ART, comorbidities, TB symptom screening results (ICF), and TPT use. Viral load (VL) data were collected from Kenya's national VL program.

Clinic survey details were previously published.[78] Briefly, a designated HCW completed a survey on clinic characteristics (type, size of clinic, number of specialized staff, HIV and TB services, adolescent-specific services, and disclosure and transition services). Healthcare workers were eligible to complete the survey if they were employed for at least 6 months and provided HIV care to YWHIV. Data were collected using Research Electronic Data Capture tools.[79]

Data analysis

Continuous data are summarized as medians and interquartile ranges (IQR), and categorical data are summarized as counts and proportions. Data were abstracted for all YWHIV attending the selected HIV

clinics during the study period. YWHIV were excluded if they reported TB symptoms at any time, had any evidence of active TB disease or were on anti-TB medication at any time, or had TPT initiation, pick-up, or completion prior to January 1, 2016 (Figure 1). TPT initiators were defined as individuals with any data regarding TPT start, collection, end date, or recorded outcome (completed, defaulted, discontinued, died, or transferred out). TPT non-initiators were defined as individuals with an ICF/IPT card but no record of receiving TPT. YWHIV were eligible for inclusion in the TPT completion analysis if they initiated TPT at least 6 months prior (June 1, 2017) to study period end date to ensure adequate time for 6 months of IPT completion within the study period. TPT completers were defined as those with TPT completion dates or "completed" TPT outcome in their medical records. TPT non-completers were defined as individuals who initiated but were not recorded as having completed TPT.

The proportions of YWHIV who initiated TPT and completed TPT (among TPT initiators) were summarized for each clinic, and median TPT initiation and completion rates across all clinics were calculated. Clinics with ≥ median TPT initiation were compared to those with rates < median TPT initiation. Pre-specified cofactors assessed included: clinic type, patient-to-staff ratio, adolescent service characteristics, interval TPT dispensed, options for proxy collection of TPT, reported TPT shortages, and percentage of YWHIV with HIV viral suppression at the clinic. Individual cofactors of TPT initiation and completion were assessed, including: age at enrollment in HIV care, sex, presumed perinatal HIV infection, marital status, received treatment support, type of treatment support person at enrollment (parent, spouse, or other), and WHO stage at the start of ART. YWHIV were presumed to have perinatal HIV infection if ART was initiated at ≤12 years of age or if the mother was diagnosed with HIV.[80] Data from the earliest visit on the HIV clinic card were utilized to describe the baseline characteristics of YWHIV. Treatment support was defined as the provision of treatment monitoring and/or social support to individuals. Individuals in polygamous or monogamous marriages were classified as married, and other marital status included those who were divorced, widowed, or cohabitating.

Bivariate analysis and multivariate generalized linear models with log link and Poisson family were used to estimate the prevalence ratio (PR) for clinic-level cofactors of TPT initiation and completion or relative risk

(RR) for individual-level cofactors of TPT initiation and completion, clustered by clinic. Bivariate results were assessed for differences between clinic and individual strata, and characteristics that were statistically significant (p-value ≤0.05) were considered for inclusion in the final multivariate model. Fisher's exact test was utilized to estimate p-values testing for significant association between groups with small sample sizes (n<5).Variables were assessed for collinearity and excluded if the variance inflation factor exceeded 6.

RESULTS

Patient Population

Overall 101 HIV clinics were enrolled, and YWHIV records were abstracted from paper and/or electronic medical records (EMR). Clinics with only EMR data (n=14) were excluded because of unavailable ICF/IPT cards (paper form). Among the 87 clinics with ICF/IPT data, 1 clinic had no YWHIV with recorded TPT initiation or completion; this clinic was excluded, leaving 86 clinics in the analysis (Figure 1). Between January 1, 2016 and December 31, 2017, 11,111 YWHIV in 86 clinics were potentially eligible based on availability of ICF/IPT data. Individuals with any TB symptoms (151; 1.4%), evidence of active TB disease or anti-TB medication (63; 0.6%), or dates for TPT initiation, collection, or completion prior to January 1, 2016 (569; 5.1%) were excluded, leaving 10,328 (93.0%) YWHIV in the cascade analysis (Figure 1). TPT initiators without at least 6 months of data following TPT initiation (1042/4337, 24.0%) were excluded from the TPT completion analyses.

TPT cascade initiation and completion

Among the 10,328 eligible YWHIV, 4337 (42.0% [95% CI:41.0-42.9%]) initiated TPT. Among 3295 TPT initiators with sufficient follow-up time, 1774 (53.8% [95% CI:52.1-55.5%]) completed TPT (Figure 2).

CLINIC CHARACTERISTICS

All 86 clinics surveyed reported the availability of TPT. Sub-county hospitals (40.7%; 35/86) were the most frequent clinic type, followed by health centers (34.9%; 30/86), county referral hospitals (11.6%; 10/86), and dispensaries (12.8%; 11/86; Table 1). The Ministry of Health was the primary clinic owner (41/86; 95.3%; Table 1). Most clinics (57.3%; 43/75) dispensed 1 month of TPT at a time. Almost all clinics permitted a proxy (typically a parent or spouse) to obtain medication (96.3%; 78/81;Table 1). Nine clinics reported TPT shortages (11.3%; 9/81); these shortages occurred between less than once a year (44.4%; 4/9) up to

monthly (11.1%; 1/9; data not shown).TPT shortages were reported to affect the prescribing patterns of TPT and resulted in a shorter duration of medication dispensed at a time (55.5%; 5/9), delayed TPT initiation until additional supplies were received (33.3%; 3/9), or gaps in TPT continuation (11.1%; 1/9; data not shown).

Across 84 clinics with available HIV VL data, the per-clinic frequency of viral suppression among YWHIV ranged from 48% to 100%, with a median clinic-level frequency of viral suppression of 72% (IQR 67-77%). Median clinic-level TPT initiation and completion among YWHIV were 50.7% (95% CI:32.3-74.2%) and 55.6% (95% CI:30.4-75.3%), respectively.

Clinic-Level Cofactors of TPT Initiation

Comparing clinics (n=86) with ≥ median TPT initiation rate to those with < median TPT initiation rate, clinics with higher TPT initiation had a lower patient-to-staff ratio than clinics with lower TPT initiation (p=0.044). Clinics with designated adolescent areas had higher TPT initiation than those that utilized adult or other clinic areas for YWHIV care (PR 2.05 [95% CI:1.46-2.88] p<0.001). Other clinic characteristics, including clinic type, interval of TPT dispensed, TPT shortages, and median viral suppression among YWHIV, were not associated with clinic TPT initiation.

Clinic-level cofactors of TPT completion

Comparing clinics ≥ median TPT completion rate (n=85 clinics; 1 clinic had no individuals eligible for TPT completion analysis) to those with < median TPT completion rate, dispensaries had a trend for the highest TPT completion compared to all other clinic-level types (PR 4.00 [95% CI:1.11-14.46] p=0.035) and clinics with designated adolescent areas had higher TPT completion compared to those that utilized adult or other clinic areas, but not significantly so (PR 1.24 [95% CI:0.76-2.00] p=0.389; Table 1). Clinics with ≥ median TPT completion rate had lower patient-to-staff ratios than those clinics with < median TPT completion rate (p=0.004).

Individual participant characteristics

Overall, the median age at enrollment in HIV care was 17 years (IQR 8-21). Most YWHIV were female (70.3%; 7184/10,216). Among 5240 YWHIV aged ≥18 years who had reported marital status, 1825 (38.7%) were single. The median duration of ART was 34 months, and most (60.6%) YWHIV were on ART for at least 2 years by January 8, 2018 (earliest data abstraction date; Table 2).

Individual-level cofactors of TPT initiation

Adolescents and young adults who were younger at enrollment in HIV care (≤14 years) were more likely to initiate TPT than those initiating care at an older age (≥15 years; RR 1.18 [95% CI:0.91-1.04] p<0.001; Table 2). TPT initiation was higher among those who were presumed perinatally infected (RR 1.18[95% CI:1.10-1.26] p<0.001) and longer ART duration (1-2 vs. <1 year RR 1.31[95% CI:1.18-1.45]. Among YWHIV ≥18 years, married (RR 1.27 [95% CI:1.07-1.50] p=0.006) or single (RR 1.21 [95% CI:1.04-1.42] p=0.013) participants were more likely to initiate TPT, compared to the "other" reference group of those who were divorced, widowed, or cohabitating. Among YWHIV ≥18 years, TPT initiation was higher among those with a designated treatment supporter than among those without (RR 1.15 [95% CI:1.01-1.30] p=0.030).

To discern the independent effects of age at enrollment in HIV care and ART duration, the multivariate model for TPT initiation included age at clinic enrollment, sex, and duration on ART. Marital status and treatment support were not included in the model because of the limited sample size (<65% of the study population). In this model, younger age at enrollment and longer duration on ART remained independently and significantly associated with TPT initiation (Table 3).

Individual-level cofactors of TPT completion

TPT completers had a lower median age at HIV care enrollment than non-completers (12 vs. 16; p<0.001; Table 2). Similarly, there was a greater proportion of YWHIV who were perinatally infected among TPT completers (RR 1.09 [95%CI:1.01-1.17] p=0.022). Additionally, TPT completion was higher among single YWHIV than among those who were divorced, widowed, or cohabitating (RR 1.36 [95% CI:1.05-1.75] p=0.020), and more likely among those with longer ART duration (2-5 vs. <1 year, RR 1.27 [95%CI:1.03-1.57] p=0.032).

The multivariate model for TPT completion included age at clinic enrollment, sex, and duration on ART. In multivariate analysis, longer duration on ART remained associated with TPT completion (2-5 vs. <1 year; RR 1.23 [95% CI:1.00-1.51] p=0.054), adjusting for age and sex (Table 3).

DISCUSSION

In this study of >10,000 YWHIV at 86 clinics in Kenya, we demonstrated substantial gaps in the TPT cascade. Despite national guidelines for HIV clinics to provide TPT, less than half of YWHIV in HIV care initiated TPT, of whom less than 60% completed TPT. Clinics with designated adolescent areas and those with lower patient-to-staff ratios had higher TPT initiation and completion. Individual cofactors of TPT initiation and completion included younger age at entry into HIV care, treatment support, perinatal HIV, and longer duration on ART. Taken together, our data demonstrate the need for improved TPT initiation and completion in YWHIV, particularly among those who enter HIV care when they are older.

HIV care settings are an ideal environment to ensure TB screening and TPT provision; however, our study suggests a disconnect between the clinic-reported universal availability of TPT and actual TPT use and completion among YWHIV at these clinics. A 2016 systematic review in predominantly high-income countries among adults noted that approximately 50% of people with medical indications (such as HIV) completed TPT.[81] Recent studies in SSA estimated TPT initiation rates of 14% to 58%[82-85] and completion rates ranging from 40% to 94%.[85-88] A recent evaluation of TPT use among children (aged <15 years) newly enrolled in HIV care in Kenya observed 68% TPT initiation and 78% TPT completion.[89] However, to date these findings have not been age-disaggregated to define the cascade in adolescents or young adults.[89] Our study suggests that there are opportunities to improve TPT initiation and completion, particularly focused on older YWHIV, more recently enrolled in clinics, and without treatment support.

A national study in Kenya found higher rates of TPT initiation (68.9%) and completion (73.5%) than we did.[72] This study utilized national data from a similar period (2015-2018) as our study, but had few YWHIV, with 85% of the study population being >25 years old. In contrast, we focused on ages 10-24 years old. Other methodologic differences included sampling approach and that TPT completion was assessed only among those with outcome data. Other studies of children with HIV <15 years of age have also found

higher rates of initiation and completion than in our study (>60 and >70%, respectively).[89, 90] However, these were smaller studies limited to <10 clinics. Overall, our findings suggest that YWHIV have worse TPT initiation and completion than adults or children with HIV. Additionally, methodologic differences in sampling and estimation suggest that there may be need to standardize the approach to evaluation of the TPT cascade in general.

Kenya's health centers provide basic primary care and have been leveraged for HIV testing and care.[91] We observed higher TPT initiation among health centers than county referral centers and hypothesized that lower volume clinics may provide additional time for education and counseling, shorter wait times, and sufficient staffing. Consistent with this hypothesis, we found that clinics with ≥ median TPT initiation or ≥ median TPT completion rates had a significantly lower patient-to-staff ratio. With greater healthcare staff and resources, previously identified barriers to HIV care (i.e., long wait times, lack of organization, and medication shortages)[27] are minimized and may result in improved engagement in both HIV care and TB prevention services. In a qualitative assessment of adolescents in HIV care in western Kenya, challenges cited by adolescents included long turnaround times, inadequate numbers of HCW, lack of privacy, and lack of adolescent days and support groups.[28] Adolescent-friendly infrastructure may not be feasible for all clinics and utilization of adolescent friendly services may be an adequate substitute depending on the needs of the population it serves.

In our survey, 11% of the clinics reported episodic shortages that affected TPT dispensing. Clinics with TPT shortages noted that they delayed TPT initiation during stock-outs. However, our clinic-level analysis had an insufficient sample size to detect a significant difference in TPT initiation and completion in clinics with shortages. We found that clinics with higher than median TPT initiation were more likely to provide 6 months of TPT than those with lower than median TPT initiation. It is possible that clinics with lower supplies (though not necessarily a shortage) dispensed fewer doses at a time and failed to initiate TPT due to concerns about TPT availability. We found a trend for lower TPT completion in clinics with shortages. Commodity management improvements are likely to enhance TPT initiation and completion.

We identified several individual cofactors for TPT initiation and completion. A younger age at HIV care enrollment was associated with TPT initiation and completion. YWHIV with perinatal HIV were more likely to initiate and complete TPT in our study, which may reflect the involvement of caregivers or well-established habits of healthcare utilization and adherence in this group of YWHIV. A previous cross-sectional study noted higher TPT initiation in adults than in children among PLHIV in Zambia; however, there was low TPT initiation overall (<25%).[82] Similarly, a mixed-methods study among children and adults living with HIV in India observed older age associated with TPT initiation, identified shortages, lack of education (for both HCW and patients), and loss to follow up as reasons for non-initiation.[83] We observed lower TPT completion than some adult studies in SSA, which may reflect differences between YWHIV and adults,[84-87] different sites of TPT delivery (such as pharmacist-initiated TPT),[22] or cohorts with more advanced disease.[84, 85] Support groups for YWHIV could facilitate messaging to improve TPT completion, mirroring effectiveness of peer groups on retention in HIV care.[92] YWHIV with longer time in care had a higher likelihood of TPT initiation and completion. With more experience in the healthcare system, this group may have better access support to navigate TPT completion. A qualitative assessment of adolescents with perinatal HIV in South Africa supports our findings, in which early HIV disclosure offered informational support deemed essential for engagement in care and medication adherence.[93]

Among older YWHIV, we found that divorced, widowed, or cohabitating individuals had a lower likelihood of TPT initiation than single or married YWHIV. Similarly, TPT initiation was lower in individuals who did not receive treatment. Lack of social support, social strain, and isolation had detrimental impacts on TPT adherence among individuals with HIV in South Africa and adults aged ≤35 years in England.[21, 94-96]

Shorter TPT options are recommended by the WHO and deemed non-inferior to longer regimens, with 3 months of rifapentine plus isoniazid weekly for use among individuals 2 and older and 1 month of rifapentine plus isoniazid daily for those 13 years and older.[2] Utilization of shorter regimens may increase completion rates but may not reduce barriers to initiation. Cost modeling would be useful for estimating the potential benefits of shorter TPT regimens among YWHIV.

A limitation of our study was the exclusive utilization of medical records for individual analyses. Programmatic data may have completeness and quality issues. Missingness was common, and we observed that up to 43% of TB symptom screenings were missing at the first visit. Therefore, it was unclear whether symptom screening was performed. The lack of consistent patient identifiers challenged the linkage to the national HIV VL database, making it impossible to incorporate individual VLs in analyses; therefore, we utilized clinic-level VL suppression. Clinic selection excluded facilities without EMRs, and therefore lacked country-wide generalizability. Clinic survey responses may have been biased towards reporting per policy rather than actual practice, and no objective assessment was conducted to confirm the reported characteristics. Lastly, our analysis did not include the time during or after the COVID-19 pandemic, and therefore does not reflect health systems changes that occurred post-2020. The strengths of our study include the considerable number of clinics and YWHIV, and the evaluation of clinic-level and individual-level factors. The focus on YWHIV is important, as this growing population has an increased risk of TB infection and disease, yet it remains understudied.

In conclusion, we found large gaps in TPT implementation, and both clinic-level and individual characteristics influenced TPT initiation and completion among YWHIV. Consistent programmatic tracking of the TPT cascade for YWHIV could increase awareness of gaps and aid in focused efforts to optimize the TPT cascade. Importantly, this will require age-disaggregated data summaries of the TPT cascade to refine approaches for children, adolescents, and young adults. The growing population of YWHIV heightens the need to implement focused strategies to best serve this population. Adolescent-specific training, adolescent-friendly clinics, and age-appropriate support for YWHIV are potential strategies to reduce gaps in TB prevention efforts. Finally, as TPT rollout continues to increase, our efforts need to focus on subsets of YWHIV that require additional support to ensure closing TPT cascade gaps.

FIGURES

Figure 1. Clinic and Patient Selection Criteria.

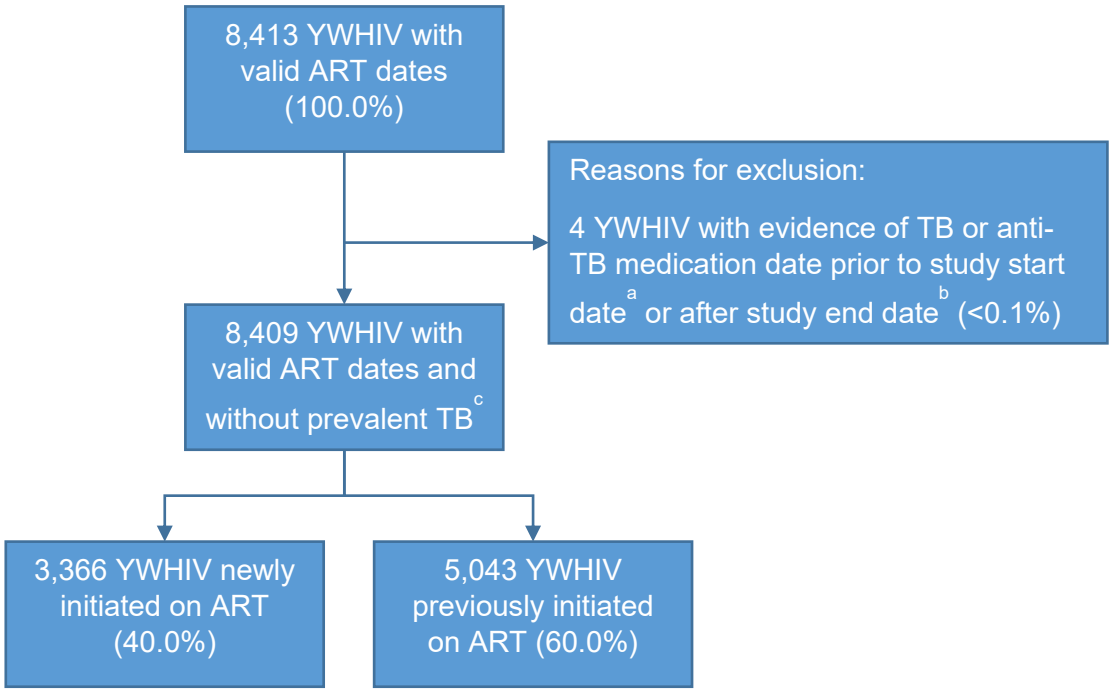
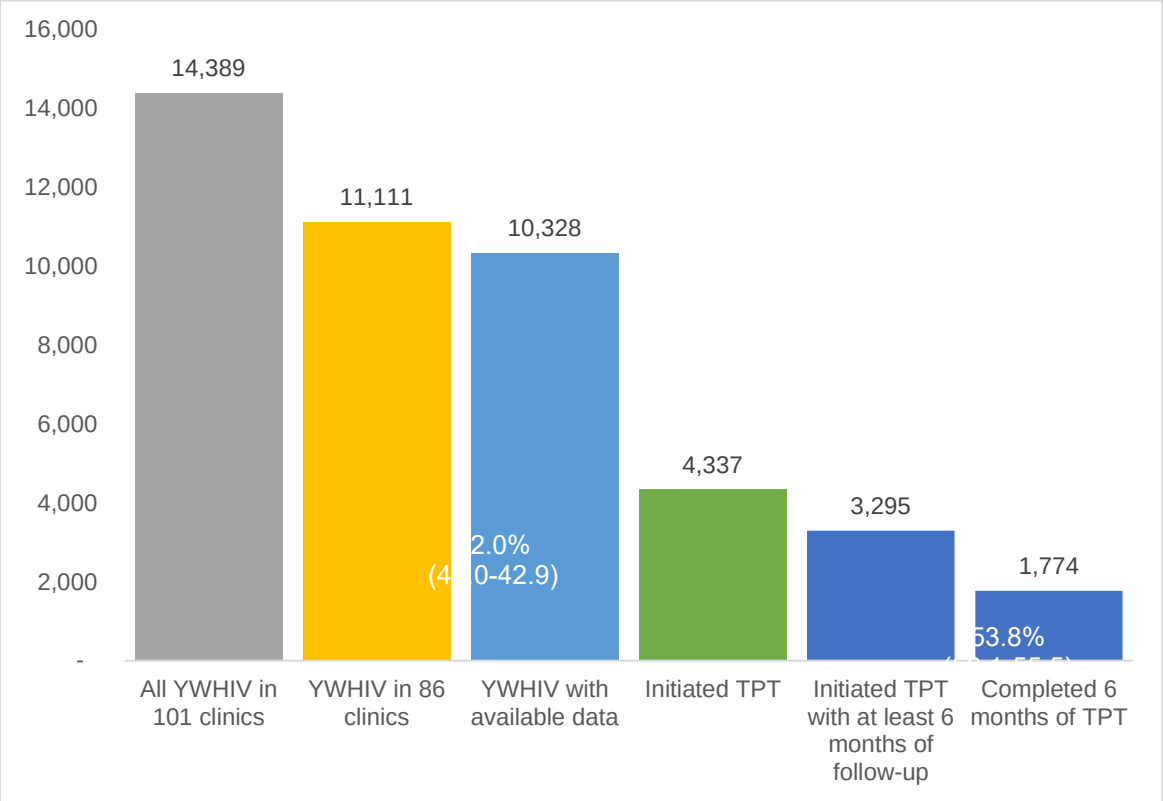


Figure 2. Tuberculosis prevention cascade of care among adolescents and young adults living with HIV (n=10,328) at 86 HIV clinics in Kenya.



Tuberculosis prevention cascade of care among adolescents and young adults living with HIV (n=10,328) at 86 HIV clinics in Kenya. TPT, tuberculosis preventive treatment; YWHIV, adolescents and young adults living with HIV. Proportions and 95% confidence intervals were calculated for each step of the cascade.

Table 1. Clinic-level predictors of TPT initiation (n=86) and completion (n=85) – bivariate models

	N	All Clinics[1] (n=86)	Clinics with < median TPT[2] initiation (n=43)	Clinics with ≥ median TPT[2] initiation (n=43)	PR[3] (95% CI)/ *P value*	N	All Clinics[1] (n=85)	Clinics with < median TPT[2] completion (n=42)	Clinics with ≥ median TPT[2] completion (n=43)	PR[3] (95% CI)/ *P value*
Clinic type	86					85				
County referral hospital		10(11.6%)	7(16.3%)	3(7.0%)	ref.		10(11.8%)	8(19.0%)	2(4.7%)	ref.
Sub-county hospital		35(40.7%)	21(48.8%)	14(32.6%)	1.33(0.47-3.76, p=0.586)		35(41.2%)	18(42.9%)	17(39.5%)	2.43(0.67-8.85, p=0.179)
Health center		30(34.9%)	10(23.3%)	20(46.5%)	2.22(0.83-5.96, p=0.112)		30(35.3%)	14(33.3%)	16(37.2%)	2.67(0.73-9.70, p=0.137)
Dispensary		11(12.8%)	5(11.6%)	6(14.0%)	1.82(0.61-5.44, p=0.285)		10(11.8%)	2(4.8%)	8(18.6%)	**4.00(1.11-14.46, p=0.035)**
Clinic ownership[4]	86				p=0.433	81				p=1.000
Faith-based organization		6(7.0%)	4(9.3%)	2(4.7%)			4(4.9%)	2(5.6%)	2(4.4%)	
Ministry of Health		79(91.9%)	38(88.4%)	41(95.3%)			76(93.8%)	34(94.4%)	42(93.3%)	
Non-governmental organization		1(1.2%)	1(2.3%)	0(0.0%)			1(1.2%)	0(0.0%)	1(2.2%)	
Patient-to-staff ratio[5]	64	52(28-81)	70(45-86)	43(23-70)	**p=0.044**	63	52(28-81)	70(45-98)	43(25-59)	**p=0.004**
Adolescent service characteristics										
Have specific staff who provide HIV care for adolescents and children	86	3(3.5%)	1(2.3%)	2(4.7%)	1.35(0.59-3.11, p=0.481)	85	3(3.5%)	2(4.8%)	1(2.3%)	0.65(0.13-3.30, p=0.604)
YWHIV in active HIV follow-up in clinic	74	46(33-111)	64(31-119)	45(36-70)	p=0.065	73	46(34-111)	51(33-124)	45(34-70)	p=0.295
Clinics with select “adolescent days”	86	70(81.4%)	32(74.4%)	38(88.4%)	1.74(0.81-3.72, p=0.156)	85	70(82.4%)	33(78.6%)	37(86.0%)	1.32(0.68-2.56, p=0.409)
Designated adolescent area in clinic	86	15(17.4%)	2(4.7%)	13(30.2%)	**2.05(1.46-2.88, p<0.001)**	85	15(17.6%)	6(14.3%)	9(20.9%)	1.24(0.76-2.00, p=0.389)
Interval TPT dispensed	75					74				
1 month		43(57.3%)	22(55.0%)	21(60.0%)	ref.		43(58.1%)	20(54.1%)	23(62.2%)	ref.
3 months		10(13.3%)	6(15.0%)	4(11.4%)	0.82(0.36-1.87, p=0.635)		10(13.5%)	6(16.2%)	4(10.8%)	0.75(0.33-1.69, p=0.484)
6 months		4(5.3%)	1(2.5%)	3(8.6%)	1.54(0.80-2.93, p=0.194)		4(5.4%)	2(5.4%)	2(5.4%)	0.93(0.34-2.61, p=0.897)
Other		18(24.0%)	11(27.5%)	7(20.0%)	0.80(0.41-1.54, p=0.498)		17(23.0%)	9(24.3%)	8(21.6%)	0.88(0.49-1.57, p=0.665)

Dispense TPT to proxy	81	78(96.3%)	42(97.7%)	36(94.7%)	0.69(0.30-1.60, p=0.391)	36	77(96.3%)	39(95.1%)	38(97.4%)	1.48(0.29-7.53, p=0.636)
Clinic reported TPT shortages	80	9(11.3%)	6(14.3%)	3(7.9%)	0.68(0.26-1.77, p=0.424)	3	9(11.4%)	6(15.0%)	3(7.7%)	0.65(0.25-1.69, p=0.375)
Average percentage of individuals with viral suppression across clinics[6]	84	72(67-77)	71(67-76)	75(64-77)	p=0.126	75	72(67-77)	71(67-77)	74(67-77)	p=0.429

Data are n (%) or median (IQR). Bold text indicates statistical significance. CI, confidence interval; IQR, interquartile range; PR, prevalence ratio; TPT, tuberculosis preventive treatment; YWHIV, adolescents and young adults living with HIV.

1. Percentages for TPT initiation among all clinics are out of 86 clinics, unless otherwise noted. Percentages for TPT completion among all clinics are out of 85 clinics, unless otherwise noted.
2. Median TPT initiation was defined as at least 38% of the individuals at a clinic initiating TB preventative therapy (IQR TPT initiation 31 – 55). Median TPT completion was defined as at least 57% of the individuals at a clinic completing TB preventative therapy (IQR TPT initiation 35 – 75).
3. Prevalence ratio compares clinics with greater than or equal to median TPT initiation/completion versus those with less than median TPT initiation/completion.
4. Fisher's exact test was used to calculate the p-value, comparing clinic ownership between TPT initiation and completion cohorts.
5. The patient to clinic staff ratio calculated the number of active individuals (adults, adolescents, and/or children) at the clinic divided by the total number of staff at the clinic.
6. Percent virally suppressed is mean value of the proportion of individuals at each clinic that are virally suppressed (defined as <1000 copies/mL) proportion of clinics that were virally suppressed among each stratum (all clinics, clinics with less than median TPT initiation/completion, and clinics with more than median TPT initiation/completion)

Table 2. Individual cofactors of TPT initiation (n=10,389) and completion (n=3295) among YWHIV – bivariate models

	N	All YWHIV[1] (n=10,328)	TPT non-initiator (n=5991)	TPT initiator (n=4337)	RR (95% CI)/ *P value*	N	All eligible YWHIV[1] (n=3295)	TPT non-completer (n=1521)	TPT completer (n=1774)	RR (95% CI) / *P value*
Age at enrollment in HIV care	9391	17(8-21)	18(9-21)	15(8-21)	**p<0.001**	2968	13(7-20)	16(8-21)	12(6-20)	**p<0.001**
14 and younger		4216(44.9%)	2246(41.2%)	1970(50.0%)	**1.18(0.91-1.04, p<0.001)**		1619(54.5%)	645(47.8%)	974(60.2%)	**1.09(1.02-1.18, p=0.017)**
15 and older		5175(55.1%)	3208(58.8%)	1967(50.0%)	ref.		1349(45.5%)	705(52.2%)	644(39.8%)	ref.
Female sex	10216	7184(70.3%)	4212(71.2%)	2972(69.1%)	0.96(0.92-1.00, p=0.062)		2199(67.2%)	1045(69.3%)	1154(65.4%)	0.98(0.92-1.04, p=0.454)
Perinatally infected[2]	9463	3807(40.2%)	2004(36.5%)	1803(45.3%)	**1.18(1.10-1.26, p<0.001)**	3002	1490(49.6%)	587(42.9%)	903(55.2%)	**1.09(1.01-1.17, p=0.022)**
Reported marital status[3]	5240					1418				
Married[4]		2548(54.0%)	1551(52.7%)	997(56.2%)	**1.27(1.07-1.50, p=0.006)**		684(55.8%)	368(57.5%)	316(54.0%)	1.18(0.95-1.48, p=0.140)
Single		1825(38.7%)	1149(39.1%)	676(38.1%)	**1.21(1.04-1.42, p=0.013)**		468(38.2%)	227(35.5%)	241(41.2%)	**1.36(1.05-1.75, p=0.020)**
Other[5]		344(7.3%)	242(8.2%)	102(5.7%)	ref.		73(6.0%)	45(7.0%)	28(4.8%)	ref.
Received any treatment support[3]	5240	4534(86.5%)	2783(86.4%)	1751(86.7%)	**1.15(1.01-1.30, p=0.030)**		1223(86.2%)	637(85.4%)	586(87.2%)	1.01(0.89-1.15, p=0.850)
YWHIV on ART[6]	10328	8552(82.8%)	4645(77.5%)	3907(90.1%)		3295	2958(89.8%)	1314(86.4%)	1644(92.7%)	
Duration on ART[7]	8524					2952				
Less than 1 year		1667(19.6%)	1050(23%)	617(15.8%)	ref.		201(6.8%)	124(9.5%)	77(4.7%)	ref.
1-2 years		1691(19.8%)	836(18%)	855(21.9%)	**1.31(1.18-1.45, p<0.001)**		693(23.5%)	361(27.5%)	332(20.2%)	1.15(0.96-1.38, p=0.140)
2-5 years		2561(30.0%)	1366(30%)	1195(30.6%)	**1.21(1.04-1.41, p=0.014)**		1010(34.2%)	426(32.5%)	584(35.6%)	**1.27(1.02-1.57, p=0.032)**
More than 5 years		2605(30.6%)	1371(30%)	1234(31.6%)	**1.25(1.09-1.43, p=0.002)**		1048(35.5%)	400(30.5%)	648(39.5%)	**1.30(1.05-1.60, p=0.015)**
WHO stage at start of ART	6366					2169				

I		3109(48.8%)	1731(49.6%)	1378(47.9%)	ref.		962(44.4%)	459(48.4%)	503(41.2%)	ref.
II		2045(32.1%)	1099(31.5%)	946(32.9%)	1.00(0.93-1.08, p=0.941)		747(34.4%)	295(31.1%)	452(37.0%)	1.07(0.99-1.16, p=0.686)
III		1105(17.4%)	600(17.2%)	505(17.6%)	1.02(0.94-1.11, p=0.580)		420(19.4%)	180(19.0%)	240(19.7%)	0.98(0.87-1.09, p=0.807)
IV		107(1.7%)	62(1.8%)	45(1.6%)	0.99(0.86-1.16, p=0.946)		40(1.8%)	15(1.6%)	25(2.0%)	1.04(0.78-1.37, p=0.807)

Data are n (%) or median (IQR). Bold text indicates statistical significance. ART, antiretroviral therapy; CI, confidence interval; IQR, interquartile range; RR, relative risk; TPT, tuberculosis preventive treatment; WHO, World Health Organization; YWHIV, adolescents and young adults living with HIV.

1. Percentages among All YWHIV are calculated out of n=10,328 for TPT initiation or n=3295 for TPT completion
2. Presumed perinatally infected was defined as individuals who initiated ART on or before the age of 12 and/or has mother with HIV.
3. Marital status and treatment supporter are presented among YWHIV at least 18 years of age and older at time of ART initiation (n=5240 age 18+ among all YWHIV and n=1418 age 18+ among YWHIV TPT initiators).
4. Married includes polygamous and monogamous marriages.
5. Other marital status includes divorced, widowed, and cohabitating.
6. YWHIV on ART defined by a date of ART initiation and/or indicated any use of ART.
7. Duration on ART (months) was calculated as the number of days between the initiation of 1st line ART regimen and January 8, 2018, which was the earliest data abstraction date.

Table 3. Individual cofactors of TPT initiation and completion among YWHIV – multivariate models

	TPT initiation[1] aRR (95% CI, p-value)	TPT completion[1] aRR (95% CI, p-value)
Age at clinic enrollment		
14 and younger	**1.23(1.13-1.33, p<0.001)**	1.06(0.98-1.15, p=0.154)
15 and older	ref.	ref.
Female sex	1.00(0.96-1.05, p=0.981)	1.02(0.95-1.09, p=0.602)
Duration in months on ART[2]		
Less than 1 year	ref.	ref.
1-2 years	**1.30(1.16-1.46, p<0.001)**	1.12(0.93-1.35, p=0.216)
2-5 years	1.15(0.97-1.37, p=0.109)	**1.23(0.99-1.52, p=0.059)**
More than 5 years	1.07(0.90-1.27, p=0.436)	1.22(0.99-1.52, p=0.065)

Data are adjusted relative risks, 95% CI, and p value. Bold text indicates statistical significance. aRR, adjusted relative risk; ART, antiretroviral therapy; CI, confidence interval; TPT, tuberculosis preventive treatment; YWHIV, adolescents and young adults living with HIV.
1. Adjusted for age at enrollment, sex, sexual activity, and duration in months on ART.
2. Duration on ART (months) was calculated as the number of days between the initiation of 1st line ART regimen and January 8, 2018, which was the earliest data collection date.

Chapter 4: Risk and cofactors of tuberculosis incidence among adolescents and young adults with HIV

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Risk and cofactors of tuberculosis incidence among adolescents and young adults with HIV: a multisite study in Kenya

Danae Black MPH, Department of Epidemiology, University of Washington, Seattle, Washington, USA

Sylvia M. LaCourse MD, MPH Departments of Medicine, Global Health, and Epidemiology, University of Washington, Seattle, Washington, USA

Irene Njuguna MBChB, MPH, PhD, Department of Global Health, University of Washington, Seattle, Washington, USA; Kenyatta National Hospital, Nairobi, Kenya

Christine M. Khosropour, MPH, PhD, Department of Epidemiology, University of Washington, Seattle, Washington, USA

Kristin Beima-Sofie PhD, Department of Global Health, University of Washington, Seattle, Washington, USA

Caren W. Mburu MBChB, MMed, MPH Department of Pediatrics and Child Health, University of Nairobi, Nairobi, Kenya

Cyrus Mugo MBChB, MPH, PhD Department of Global Health, University of Washington, Seattle, Washington, USA; Kenyatta National Hospital, Nairobi, Kenya

Janet Itindi, Kenya Medical Research Institute, Nairobi, Kenya

Alvin Onyango, Department of Pediatrics and Child Health, University of Nairobi, Nairobi, Kenya

Barbra A. Richardson PhD, Departments of Global Health and Biostatistics, University of Washington, Seattle, Washington, USA

Dalton Wamalwa MBChB, MMed, MPH Department of Pediatrics and Child Health, University of Nairobi, Nairobi, Kenya

Grace John-Stewart MD, PhD, Departments of Epidemiology, Medicine, Global Health, and Pediatrics, University of Washington, Seattle, Washington, USA

Corresponding Author: Danae Black, danaesb@uw.edu, Department of Epidemiology, University of Washington, UW Box #351619, Seattle, WA 98195

Abstract:

Background: We lack data regarding risk of tuberculosis disease (TB) among adolescents and young adults living with HIV (YWHIV), despite known vulnerabilities to TB in this age group.

Methods: This observational study used medical record data from 86 HIV clinics throughout Kenya; abstracted data was from January 1, 2016 to January 18, 2018. Incidence rates (IR) were calculated (from time of antiretroviral [ART] initiation among those who newly initiated ART and from time of data abstraction for those previously on ART). Cox proportional hazard regression was conducted to assess covariates of TB among YWHIV who newly initiated ART and those previously on ART.

Findings: Among 8,409 YWHIV, 3,366 (40%) newly initiated ART and 5,043 (60%) were already on ART (median duration 3 years). Over the follow-up period, 53 YWHIV had a new TB diagnosis (23 newly on ART and 30 previously on ART). TB incidence was higher among YWHIV who newly initiated ART than among those previously on ART (776 versus vs. 312/100,000 person years; incidence rate ratio: 2.5 [95% CI 1.4–4.4]).

Among those who newly initiated ART, utilization of TB preventative therapy (TPT) was significantly lower in those who developed TB than those who did not (4.3% vs. 40.6%; p<0.001). Similarly among previously on ART, TPT use was associated with lower risk of TB (HR 0.42 [95% CI 0.17-1.02] p=0.055). Among YWHIV who newly initiated ART ≥18 years, having a treatment supporter was associated with a lower TB risk (HR 0.19 [95% CI 0.07-0.55] p<0.01). YWHIV ≥18 years previously on ART had lower risk of TB if they had a partner who tested for HIV (HR 0.15 [95% CI 0.06-0.42] p<0.01) or were married (HR 0.20 [95% CI 0.04-1.01] p=0.05).

Interpretation: YWHIV had a high incidence of TB, particularly those newly initiating ART. TPT use was protective and interpersonal factors influenced TB incidence perhaps due to support for TPT. Age-disaggregated data will be useful to define TB determinants and to optimize TB prevention in YWHIV.

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Background

Tuberculosis (TB), a preventable and curable disease, remains one of the leading causes of death worldwide.[1] TB continues to be the primary cause of morbidity and mortality among people living with HIV (PLWHIV), with up to 18-fold increased risk of TB disease compared to individuals without HIV.[97] Adolescents and young adults, aged 10 to 24 years of age, make up a growing proportion of PLWHIV and require tailored medical care.[69, 98] Further, young people over the age of 10 have a heightened risk of TB, due to multiple factors such as hormonal changes, social interaction, and time spent in schools and vehicles, compared to younger children.[21] Despite the joint deleterious effects of HIV and TB during adolescence, the factors influencing TB disease progression in this age group are poorly understood.[21]

Kenya remains in the top 30 countries with high TB/HIV burden.[1] In 2016, Kenya conducted a national TB prevalence study among adults aged 15 and older and identified a TB prevalence to notification ratio of 2.5 TB cases detected during the 2016 National TB survey to every 1 TB case notified and reported to the national surveillance system.[99] This discrepancy led to an upward revision of Kenya's estimated TB incidence by the World Health Organization (WHO) to 319 per 100,000 in 2017.[100] Kenya provides integrated HIV and TB services, ensuring TB screening, diagnosis, and initiation of ART for individuals with TB who test positive for HIV.[101, 102]

In 2021, approximately 20% of PLHIV in Kenya were adolescents and young adults aged 15-24.[103] Several barriers to HIV care exist for YWHIV, including access to HIV testing, lack of adolescent-specific or -friendly services, stigma, and clinic availability.[104] Once engaged in care, ART adherence can be low for YWHIV, which impedes the continuity of care and heightens their risk of detrimental health outcomes.[105] Importantly, ART and TPT reduces the risk of TB.[28, 106, 107] Current TB estimates lack age-disaggregated data for adolescents and young adults. Understanding the risk and determinants of TB in YWHIV attending HIV care is important to tailor interventions for this group. In this analysis aimed to quantify TB incidence estimates and cofactors of TB amongst YWHIV in Kenya previously on and newly initiating ART..

Methods

Study design

In preparation for a cluster randomized trial (the Adolescent Transition to Adult Care for HIV-infected Adolescents in Kenya [ATTACH]), we conducted a national survey of HIV clinics throughout Kenya.[78, 108] One hundred and two clinics were randomly selected amongst eligible facilities with electronic medical records in Kenya, and we selected a subset of these clinics which had manually abstracted data to ensure equal data completeness. Medical records for YWHIV aged 10 to 24 were manually abstracted from January 1, 2016 to January 18, 2018 (hereafter, data abstraction period). We conducted a retrospective cohort analysis using data from these select HIV clinics in the ATTACH study to estimate TB incidence and cofactors associated with TB during the data abstraction period. Abstracted variables included demographic information, HIV clinical data, ART initiation, co-morbid conditions, TB symptoms, TB treatment, and TB preventative therapy use.

Study population

Individuals were included in the analysis if they were enrolled at one of the 86 clinics and aged 10 to 24 years of age at date of data abstraction. All YWHIV initiated ART and had ART dates prior to or during the abstraction period (hereafter “valid ART dates”). YWHIV were excluded if date of TB diagnosis or anti-TB medication use occurred outside of the data abstraction period (

). We separately assessed TB incidence and cofactors of TB among new ART initiators and those were previously on ART. New ART initiators were identified as YWHIV who initiated ART on or after the start of the data abstraction period. Previous ART users were YWHIV who initiated ART prior to the data abstraction period.

Ethical considerations

The study was approved by the University of Washington Institutional Review Board (IRB) and the Kenyatta National Hospital/University of Nairobi Ethical Review Committee (ERC). Additional approval was obtained

from the National AIDS and STI Control Program, County Departments of Health and managers of participating clinics. Consent was waived by both the IRB and ERC.

Data analysis

In our primary analysis we estimated the incidence of TB among YWHIV, overall and stratified by YWHIV newly initiated on ART and previously on ART. Individuals were identified as having TB if they had a TB diagnosis or utilized anti-TB medication (other than TPT) during the data abstraction period (January 1, 2016 to January 18, 2018). The date of TB diagnosis or earliest date of initiation of anti-TB medication was defined as the date of TB for the incidence rate per 100,000 person-years (PY). Person-time to TB was analyzed from the ART start date to the TB date among YWHIV newly initiated on ART. Person-time was calculated from the start of the data abstraction period (January 1, 2016) to the TB date among previous ART users. Individuals were censored at date of loss to follow-up, death, or end of follow-up period, whichever occurred first.

Our secondary objective was to identify co-factors of TB among YWHIV, stratified by YWHIV newly initiated on ART and previously on ART. Individual characteristics of YWHIV assessed included age at clinic enrollment (continuous and categorized as 10-14, 15-19, and 20-24 years), sex (male or female), BMI, TB prevention therapy (evaluated prior to TB diagnosis, if applicable), TB symptoms, TB contacts, cotrimoxazole dispensed, and having a family member with HIV. Characteristics that were evaluated among individuals 18 years and older included having a partner tested for HIV, marital status (married, single, other), and presence of treatment support. Data from the earliest visit on the HIV clinic card during the data abstraction period was utilized to describe baseline characteristics of YWHIV. Treatment support was defined as treatment monitoring and/or social support provided by family or friends to PLWHIV. Individuals in polygamous or monogamous marriages were classified as married and other marital status included those who were divorced, widowed, or cohabitating.

Continuous data was summarized as medians and interquartile ranges (IQR) and categorical data was summarized as counts and proportions. The incidence was calculated per 100,000 person years and

reported for the overall YWHIV population and stratified by new ART initiators or previously on ART groups. The incidence rate difference and incidence rate ratio were calculated comparing YWHIV who newly initiated ART to those previously on ART. Univariate and multivariate Cox proportional hazards models were used to estimate the hazard ratio (HR) for individual characteristics of TB disease, clustered by clinic. Characteristics were considered for incorporation into the multivariate models if a p-value was $\geq$0.20. Sex was selected as a pre-specified characteristic in the multivariate models due to known biological differences in TB between males and females. Covariates with too few TB cases were not eligible for inclusion in the model. Schoenfield residuals were used to evaluation proportionality of the Cox proportional hazards models; if the tests result in p-values greater than 0.05, we assumed the proportionality assumptions were not violated.

Findings

Among 8,413 YWHIV had valid ART dates, of whom 4 were excluded due to TB diagnosis or anti-TB medication use prior to or after the data abstraction period and 8,409 were eligible for inclusion in the analysis. Among 8409 YWHIV, 3,366 (40.0%) were newly initiated on ART and 5,043 YWHIV were previously initated on ART (60.0%;Figure 1). Among all 8,409 eligible YWHIV, median age at HIV clinic enrollment was 18 years, with 80% of the evaluated YWHIV aged 15 to 24 at clinic enrollment. Most were females (73%), almost half had utilized TPT (46%), and most reported a family member with HIV (58%). Among individuals 18 years and older, more than half had a partner who tested for HIV (58%), were married (56%), and received treatment support (90%). Overall, during the 2 year data abstraction window, 53 YWHIV were identified as having TB.

TB incidence

Among 8,409 YWHIV, 53 (0.6% or 630 per 100,000 persons) had TB with an estimated TB incidence of 421 per 100,000 PY (95% CI 322 – 551). TB incidence was higher among YWHIV newly initiated on ART (776 per 100,000 PY; 95% CI 516-1,169) compared to YWHIV who previously initiated ART (312 per 100,000 PY; 95% CI 218-446), with an incidence rate ratio of 2.5 (95% CI 1.4-4.4; Table 1). Some YWHIV

newly on ART were diagnosed with TB concurrent with ART initiation (9 [39.1%]) which contributed to the risk difference. In sensitivity analyses excluding these 9 cases among YWHIV newly initiated on ART, the IR would be 473 per 100,000 (95% CI 279.9-798.0).

The cumulative incidence of TB disease was lower during the follow-up period among those previously on ART than those newly initiating ART (Figure 3). New initiators of ART had particularly high risk of TB within the first year of follow-up, with a steeper slope and consistently higher incidence over time. Of note, the newly initated on ART group does not start at zero because 9 individuals were diagnosed with TB on the same day as ART initiation.

Cofactors of TB disease among YWHIV who newly initiated ART

We evaluated characteristics of YWHIV who newly initiated ART associated with TB disease. Individuals who newly initiated ART had a median age at enrollment into HIV care of 22 years (IQR 19-23). There was a trend for lower risk of TB among females (HR 0.43 [95% CI 0.17-1.09] p=0.076;Table 2). As expected, TB disease was associated with lower BMI and presence of TB symptoms (BMI HR 0.82 [95% CI 0.75-0.91] p<0.001; TB symptoms HR 21.48 [95% CI 8.55-53.99] p<0.001; Table 2). Use of TPT was associated with an over 80% decrease in TB (HR 0.18 [95% CI 0.05-0.64] p=0.008). Among YWHIV 18 years of age and older, the presence of a treatment supporter and being married (vs. other marital status) resulted in a decreased likelihood of TB disease (treatment supporter HR 0.19 [95% CI 0.07-0.55] p=0.002; married HR 0.40 [95% CI 0.04-4.01] p=0.439).

Univariate HRs and previously established associations were utilized to select the model covariates. Covariate selection included partner testing and presence of treatment supporter; therefore, the multivariate analysis was exclusively among YWHIV 18 years or older. Among YWHIV newly initiated on ART, in analyses adjusting for partner testing for HIV and treatment supporter, there was a 74% decreased probability of TB disease among YWHIV with a treatment supporter (HR 0.26 [95% CI 0.07-0.93] p=0.038; Table 3) adjusting for female sex and partner tested for HIV.

Cofactors of TB disease among YWHIV who previously initiated ART

Among individuals who previously initiated ART, the median age at enrollment into HIV care was 14 years of age (IQR 8-20) and was similar between those who did and did not develop TB. Lower BMI (HR 0.90 [95% CI 0.82-0.99] p=0.024) and higher proportion of TB symptoms (HR 15.47 [95% CI 7.60-31.47] p<0.001) were associated with TB (Table 2). Less than half of individuals previously on ART utilized TB prevention therapy (TPT), with a lower proportion of TPT use among individuals who developed TB compared to YWHIV without TB (30.0% vs. 49.1%; HR 0.42 [95% CI 0.17-1.02] p=0.055). YWHIV who were 18 years of age and older with partners who tested for HIV had a lower probability of TB disease (HR 0.15 [95% CI 0.06-0.42] p<0.001).

Other covariates that were evaluated for inclusion in the multivariate model included female sex (HR 0.97[95% CI 0.48-1.97] p=0.933) and treatment supporter (HR 0.47 [95% CI 0.12-1.87] p=0.283; Table 2Table). Final covariate selection included partner testing, presence of treatment supporter, TB preventive therapy.

Among YWHIV who previously initiated ART, there was a 83% decreased probability of TB disease among those whose partners tested for HIV, compared to those without partners who tested for HIV while adjusting for sex and the presence of a treatment supporter (aHR 0.17 [95% CI 0.04-0.72] p=0.016; Table 3). Additionally, there was a 90% decreased risk of TB among individuals who utilized TPT compared to those who did not, when adjusted for female sex, partner tested for HIV, and the presence of a treatment supporter (aHR 0.10 [95% CI 0.01-0.87] p=0.037; Table 3Table).

Interpretation

In this large study of >8000 YWHIV at 86 clinics in Kenya, the incidence of TB was estimated 630 per 100,000 persons. This was more than double the overall (251 per 100,000 persons) in Kenya in 2021.[1] We found a significantly higher incidence of TB among YWHIV who newly initiated ART than in those already on ART (776 vs. 312 per 100,000 PYs), similar to adult studies.[106, 109, 110] Although ART use

decreases TB incidence due to immune recovery, there remained appreciable TB incidence among YWHIV already on ART (>300/100,000 PY). Our findings underscore the need for vigilant TB screening among YWHIV both newly initiating on ART, as well as for YWHIV already on ART. Encouragingly we found evidence of protective effect of TPT use in this analysis of programmatic data. A variety of other factors influenced risk of TB, including treatment supporter, marital status, partner HIV testing and female sex. These characteristics warrant further evaluation as we continue to develop TB prevention strategies that best serve the needs of youth and young adults.

It has been previously established that ART reduces the risk of TB when comparing individuals with HIV and those without. In a previous study among adolescents with perinatal HIV there was a 2.2 per 100 person-years TB incidence compared to only 0.3 per 100 person-years among adolescents without HIV, with an incidence rate ratio of 7.4 (95% CI 1.0-53.6).[111] A meta-analysis found a decreasing risk of TB associated with increasing duration on ART, with overall TB incidence higher than our findings.[110] Studies among children have demonstrated a similar trend in lower TB risk among individuals who were on ART for a longer period of time.[112, 113] It is important to implement TB preventative strategies at the time of HIV diagnosis and ART initiation.

Utilization of TPT has demonstrated a protective effect from TB disease[114, 115]; with some mixed evidence for children with HIV on ART.[116] There is a lack of age-disaggregated data on TPT use among adolescents and young adults. In the ATTACH cohort, we previously found only 42% of eligible YWHIV initiated TPT, of whom only 53% completed TPT.[108] Other programmatic studies have higher TPT utilization and completion but lack adolescent and young adult data.[72,117] As shorter TPT regimens are scaled up, it will remain important to understand unique drivers of TPT use and completion among YWHIV.

We found a trend for a higher TB risk among males than females, consistent with global data.[118] Age at enrollment in HIV care is different between males and females and this might also contribute to the observed association with higher TB risk among males who newly initiated ART. An interaction between age and sex was observed in a Brazilian study amongst household contacts of TB cases, with an increase in TB infection at a younger age in females (5-14 years) and slight increase in infection for males aged 15-39. [119]

Considerations of age and sex at the time of enrollment into HIV care may assist in evaluating TB risk and emphasize the importance of TPT use, especially among higher risk individuals.

Treatment support plays an integral role in both HIV and TB care, however how support persons impact risk of TB was of particular importance to this study. We hypothesized that treatment support would differ by age, and therefore evaluated this only among individuals over 18. Among older adolescents who newly initiated ART, treatment support was protective against TB disease. A recent meta-analysis evaluated the impact of peer support across 219 studies and found peer support beneficial for ART adherence,[120] which is an important preventive approach to the development of TB disease.[121] However in a qualitative study of HIV and TB co-infected patients in Nigeria, family support was considered both a facilitator and deterrent of treatment adherence. Participants cited family and friend support as helpful for nutritional and feeding support and for reminders to take drugs; however, needing financial support and perceived stigmatization can impede the benefits of family support.[122] It would be advantageous to evaluate YWHIV relationships across all age groups to treatment supporters and qualitatively assess the influence of treatment supporters on utilization of TB prevention therapy and awareness of TB risks.

Partner testing for HIV among individuals who previously initated ART was associated with a decreased risk of TB. With partner testing serving as a proxy for both disclosure of HIV status and support from a partner, this insight highlights the importance of a supportive partner in healthcare seeking behavior. Partners who provided social support were more likely to be disclosed to, based on a sample of women living in Los Angeles, California.[123] There are several studies that demonstrated beneficial impact of partner testing alongside prevention of mother to child transmission, including HIV-free survival for infants born to HIV-positive mothers[124], ART adherence[125], and utilization of PMTCT services.[125] These findings support the intertwined nature of partnerships and support.

Limitations of our study include the utilization of programmatic medical records, which can lack completeness and other quality issues. Tuberculosis was not laboratory confirmed for all cases; conversely, we identified tuberculosis cases through a compilation of variables indicative of TB disease or utilization of anti-TB medication. Accurate dates were important in evaluating time to TB and therefore YWHIV were

excluded if dates for ART initiation or TB diagnosis (among individuals with TB) were missing. Additionally, inclusion into our study does not capture individuals who died or were lost to follow up outside of the two-year data abstraction period, leaving our analysis subject to survivor bias. Our analysis did not include time during or after the COVID-19 pandemic and therefore does not reflect the post-2020 health system changes. Importantly, our study spanned the country of Kenya and represents substantial number of YWHIV attending HIV clinics. Although research among adolescents and young adults is a growing area for HIV, TB, and global health research, it remains understudied yet highly important to future health implications.

In conclusion, TB incidence is high among YWHIV, particularly those newly initiating ART. Treatment supporters may improve ART and TPT adherence, retention in care, and ultimately decrease TB risk. Although YWHIV who previously initated ART are at a lower risk, they were at higher risk than the general population of Kenya. The integration of HIV partner testing and counseling can potentially improve disclosure among partners, sense of support, and risk of TB. A wholistic approach will be useful to optimize TPT use and TB prevention among YWHIV.

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Contributors

DB assisted with data collection, conducted data analysis, accessed and verified data, and drafted the original manuscript. GJ-S and DW obtained funding and conceptualized and designed the parent study. GJ-S and SML provided supervision and mentorship for DB and assisted in drafting the original manuscript. INN assisted with data curation and accessed and verified data analyses. DB, INN, KB-S, CWM, CM, JI, AO, DW, BAR, and GJ-S designed data collection tools. AO coordinated data collection. JI provided administrative oversight. CWM and CM coordinated study implementation and provided operational oversight. BAR provided guidance on data analysis. All authors reviewed and approved the final manuscript.

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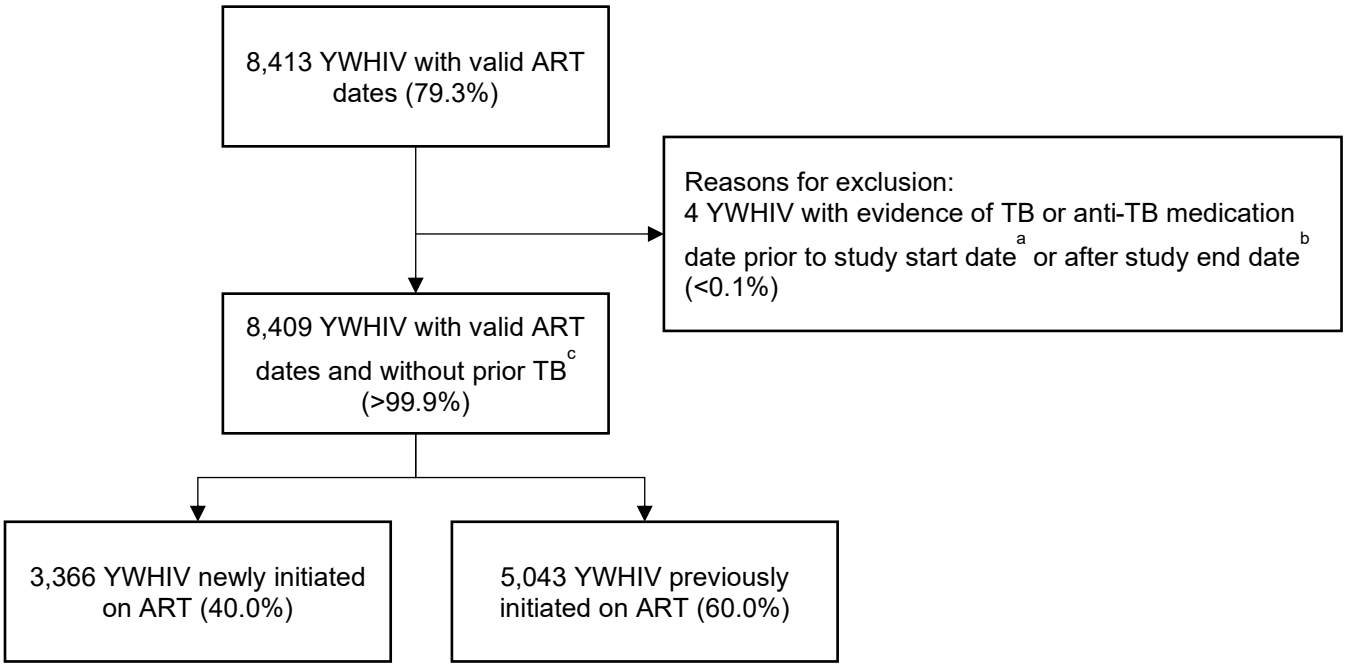
Tables and figures

Figure 1. Cohort selection



[a]Data abstraction period start date was January 1, 2016

[b]Data abstraction period end date was January 18, 2018

[c]Age was evaluated on January 1, 2016 for YWHIV who previously initiated ART and was evaluated at enrollment into HIV clinic among YWHIV newly initated on ART.

Figure 2. Study analysis schema

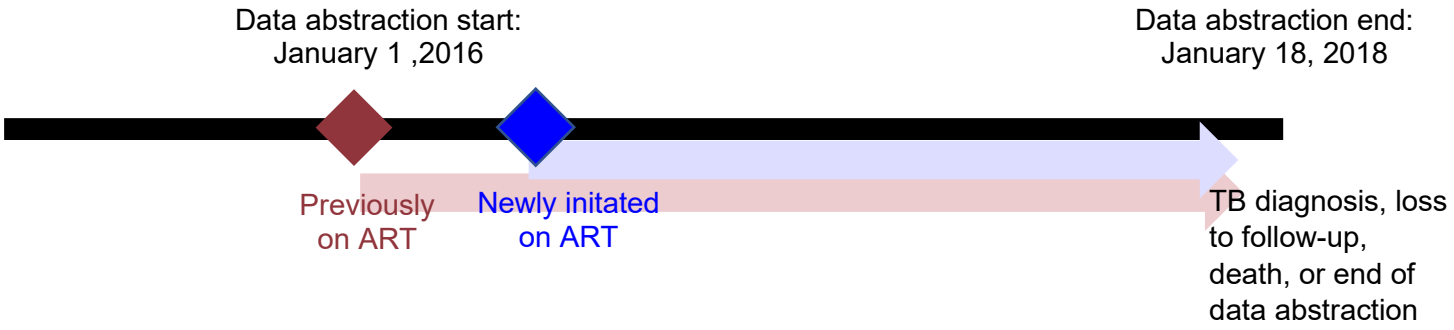


Table 1. Incidence rates, overall and by cohort

	Incidence rate (per 100,000 person-years)	**TB**	**Person time (years)**
Overall N=8,409	421 (322 - 551)	53	12,585
Previously on ART n=5,043	312 (218 - 446)	30	9,623
Newly Initiated ART n= 3,366	776 (516 – 1,169)	23	2,962
Incidence rate difference	464.7 (128.4-801.1)		
Incidence rate ratio	2.5 (1.4-4.4)		

Table 2. Characteristics of YWHIV with and without TB, by newly initated ART and previously on ART, assessed at HIV care initiation.

	Newy initiated ART				Previously on ART			
	N	No TB (n=3,366)	TB (n=23)	HR (95% CI, p-value)[1]	N	No TB (n=5,043)	TB (n=30)	HR (95% CI, p-value)[2]
Age at enrollment into HIV care, median (IQR)	3,248	22(19-23)	22(18-24)	p=0.668	4,826	14(8-20)	13(9-18)	p=0.844
less than 9						1,706(35.6%)	10(35.7%)	ref.
10 to 14		356(11.0%)	2(8.7%)	ref.		899(18.7%)	7(25.0%)	1.35(0.49-3.72, p=0.567)
15 to 19		754(23.4%)	7(30.4%)	1.68(0.32-8.83, p=0.541)		1,064(22.2%)	5(17.9%)	0.84(0.34-2.10, p=0.715)
20 to 24		2115(65.6%)	14(60.9%)	1.27(0.25-6.30, p=0.773)		1,129(23.5%)	6(21.4%)	0.97(0.35-2.66, p=0.948)
Female sex, n(%)	3,341	2,702(81.4%)	15(65.2%)	0.43(0.17-1.09, p=0.076)		3,322(66.8%)	19(65.5%)	0.97(0.48-1.97, p=0.933)
BMI, mean(SD)	2,954	21(19-24)	19(17-21)	**0.82(0.75-0.91, p<0.001)**	3,985	19(16-22)	18(15-20)	**0.90(0.82-0.99, p=0.024)**
TB prevention therapy, n(%)	3,366	1,358(40.6%)	1(4.3%)	**p<0.001**	5,043	2,459(49.1%)	9(30.0%)	**0.42(0.17-1.02, p=0.055)**
TB symptoms, n(%)	3,087	124(4.0%)	10(50.0%)	**21.48(8.55-53.99, p<0.001)**	4,098	93(2.3%)	7(28.0%)	**15.47(7.60-31.47, p<0.001)**
TB contact, n(%)	269	3(1.1%)	0(0.0%)	p=0.268	1,173	2(0.2%)	0(0.0%)	p=1.000
Cotrimoxazole dispensed, n(%)	3,111	3,078(99.5%)	19(100.0%)	p=1.000	3,946	3,899(99.4%)	23(95.8%)	p=0.137
HIV positive family member, n(%)	1,625	811(50.0%)	1(50.0%)	1.00(0.06-16.13, p=1.000)	2,012	1,274(63.7%)	7(53.8%)	0.65(0.21-1.99, p=0.446)
Partner tested for HIV[3], n(%)	1,587	812(51.5%)	7(63.6%)	1.65(0.48-5.59, p=0.425)	1,483	964(65.6%)	3(23.1%)	**0.15(0.06-0.42, p<0.001)**
Any marital status[3,4], n(%)	2,395				2,285			
Married[2]		1,373(55.1%)	3(21.4%)	0.40(0.04-4.01, p=0.439)		1,226(54.0%)	3(21.4%)	**0.20(0.04-1.01, p=0.052)**
Single		828(33.2%)	10(71.4%)	2.26(0.42-12.10, p=0.343)		873(38.4%)	9(64.3%)	0.83(0.25-2.79, p=0.768)
Other[5]		180(7.2%)	1(7.1%)	ref.		172(7.6%)	2(14.3%)	ref.
Any treatment support[3], n(%)	2,510	2,240(89.8)	10(62.5)	**0.19(0.07-0.55, p=0.002)**	2,498	2,245(90.5)	13(81.3)	0.47(0.12-1.87, p=0.283)

1. Univariate hazard ratios and associated p-values compared individuals with no TB and with TB, among YWHIV newly initated on ART
2. Univariate hazard ratios and associated p-values compared individuals with no TB and with TB, among YWHIV previously on ART
3. Partner testing, marital status, and treatment supporter are presented among YWHIV at least 18 years of age and older at time of ART initiation
4. Married includes polygamous and monogamous marriages.

5. Other marital status includes divorced, widowed, and cohabitating.

Figure 3. Cumulative incidence of tuberculosis disease among YWHIV, by individuals already on ART and newly initiated on ART.

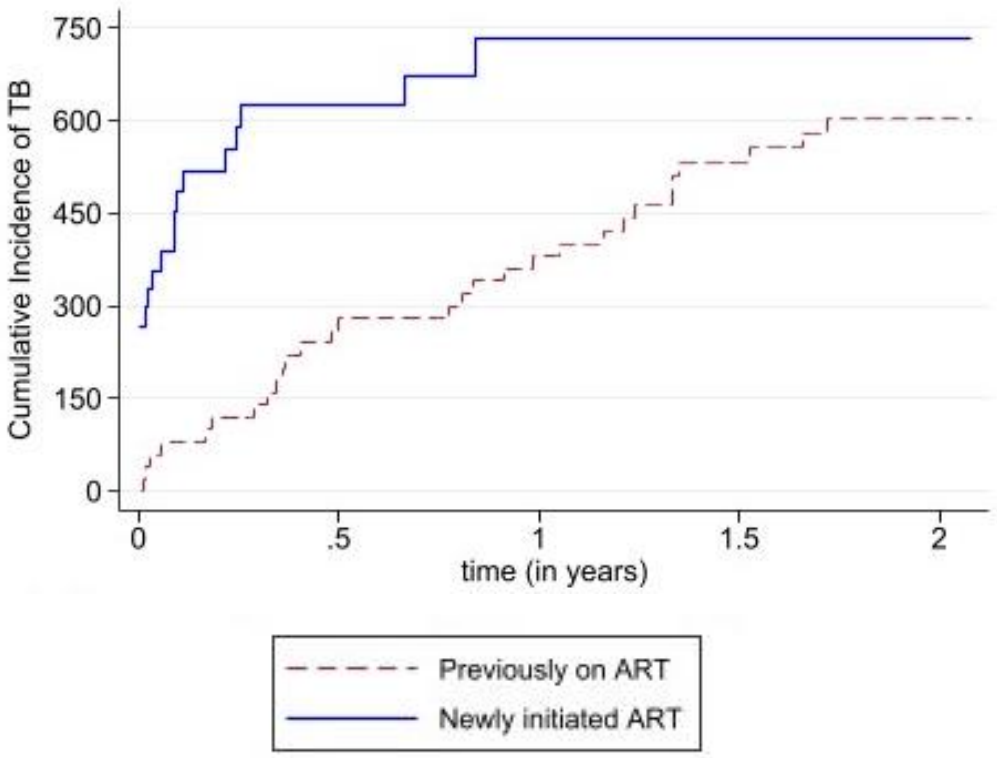


Table 3. Multivariate cox regression model estimates, among 18+ year olds

	Newly initiated ART	Previously on ART
	n=1,412	n= 1,077
	aHR (95% CI); p-value	aHR (95% CI); p-value
Female sex	**0.36 (0.15-0.89) p=0.026**	1.31(0.27-6.40) p=0.736
Partner tested for HIV	1.76 (0.54-5.69) p=0.346	**0.17(0.04-0.72) p=0.016**
Has a treatment supporter	**0.26 (0.07-0.93) p=0.038**	0.34(0.07-1.73) p=0.195
TB preventive therapy		**0.10 (0.01-0.87) p=0.037**

Chapter 5: Discussion

Discussion:

Tuberculosis risk and prevention among domestic and global cohorts

This dissertation illustrates the wealth of knowledge to be gleaned from existing accessible data sources. We evaluated TB screening and prevention activities designed to decrease TB burden and overall TB risk. In Chapter 2, the Washington State Department of Health data provided insight on non-U.S. born individuals, who have the highest prevalence of TB disease in Washington state compared to U.S. born residents. The application of Poisson regression modeling and leveraging U.S. Census data provided a unique perspective on country of origin and time since U.S. entry as TB risk factors specific to the non-U.S. born residents of Washington state. These approaches could readily be applied to other states to ensure a greater understanding of TB risk among non-U.S. born populations. Previous analyses conducted on the national level aligned with our approach and findings[5]; however, the incorporation of WHO incidence categories and appropriate weighting to fully utilize the multiple years of available TB data further elevated the distinctiveness of our analysis.

The analyses in Chapters 3 and 4 employed programmatic data and similarly offered insight into real-world application of TB prevention, TB screening, and TB diagnosis programs among YWHIV already on and newly initiating ART. The application of generalized linear modeling and time-to-event data analysis provided important insight into TB prevention and diagnosis among YWHIV, the largest cohort of YWHIV to the best of our knowledge. These approaches also allowed for clustering on the clinic level, accounting for clinic as a group-level factor. Like Chapter 2, the importance of leveraging programmatic data provides a blueprint for applying this approach to other clinics in Kenya, throughout the African continent, and throughout the world to identify and monitor gaps in TB/HIV care. Poor TPT utilization, as reported in the 2022 Global TB Report[1] among PLHIV in Kenya, needs continued monitoring and particular focused attention for adolescents and young adults (aged 10-24).

Interpretation of findings on TB risk among non-U.S. born individuals

The analysis in Chapter 2 supports utilizing country of birth as a risk factor for TB among non-U.S. born individuals in Washington state and highlights the heightened risk that remains 10 to 20 years following

date of U.S. entry. Our findings align with previous research and approaches,[5] with the utilization of the same denominator data source of the ACS public use microdata sample from the U.S. Census. Momentum towards TB elimination in the U.S. requires focused efforts to stop the increasing trend in the proportion of TB cases among non-U.S. born individuals who remain at risk many years after moving to the U.S. Our results point to a continued need for TB infection screening and treatment to prevent the persistence of TB disease with the United States.

Future directions for TB risk among non-U.S. born individuals

Opportunities to engage with care are of utmost importance shortly after immigration, where the highest rates of TB were observed; however, it is also important to ensure continued access to TB screening, diagnosis, and care as necessary. Global TB efforts utilize TB symptom screening and leverage community health workers and centers and emulation in the U.S. may provide a less stigmatizing experience for non-U.S. born individuals.[126] Additionally, the incorporation of individual characteristics into a TB risk profile model would further the applicability in a clinical care setting. Future analyses could incorporate molecular genotyping to understand the potential connectedness of non-U.S. born communities and countries of origin. These analyses could also provide insight into the prevalence of TB reactivation versus new TB infections among non-U.S. born individuals. Lastly, causal inference techniques can be used to evaluate differences in TB risk associated with changes in U.S. immigration policies and provide insight into the impact of screening or other protective strategies to minimize TB disease.

Interpretation of findings of TPT and TB risk among YWHIV in Kenya

The analyses in Chapters 3 and 4 jointly support the need for greater utilization of TPT and the need to prioritize TB prevention among YWHIV. The age differences observed in both analyses highlight the differences across the age 10 – 24 age group and highlight the importance of diverse and age-specific clinic services and support systems. These analyses contribute vital data and results to the intersection of TB, HIV, and adolescent health research. Tuberculosis further perpetuates social inequities and filling the gap in understanding adolescent health, TB prevention, and TB diagnosis is an important step towards minimizing its impact among this particularly vulnerable population. High TB incidence observed in Chapter 4 additionally highlights the lost details in TB risk that occurs when data are aggregated by children (<15

years) and adults (≥15 years). This research was particularly impactful due to the diversity of the clinics included in the analysis and Kenya's position as a high HIV/TB burden country, making these results and their approaches generalizable to other countries with HIV/TB co-epidemics. To the best of our knowledge, there is no other evaluation of TPT among YWHIV aged 10-24, particularly in such a sizable cohort. The large sample size allowed us to observe differences in individual characteristics by TPT utilization and occurrence of TB disease. Although there were few clinic characteristics that were significantly different by median TPT initiation and completion, important trends in clinic types, adolescent services, and TPT shortages were all important considerations to be shared with participating clinics.

Future directions for TPT and TB risk among YWHIV in Kenya

TB prevention, despite the 2016 country wide roll out in Kenya, needs significant improvements. Our analyses presented data prior to the COVID-19 pandemic; however, drops in TPT utilization among TB contacts highlight setbacks incurred during the pandemic.[127] The results from our findings should inform approaches to increase TPT use in HIV clinics among YWHIV. Additional qualitative analyses to discern clinic and individual perspectives on TB prevention would help develop services to serve the needs of YWHIV. In a qualitative analysis adolescents reported stigma from health workers and healthcare workers' perceived low risk for TB for adolescents amongst reasons for missed TB diagnosis.[128] The utilization of shorter and equally effective TPT regimens may offer a more acceptable and accessible alternative in the coming years.[129] It will be important to evaluate the effectiveness and rates of completion of shorter TPT regimens among YWHIV, to determine if we similar TPT initiation, completion, and change in risk of TB as observed in adult populations.[130] An important aspect to utilizing programmatic data is returning results to communities. This will be coordinated with the ATTACH study team to ensure participating clinics are aware of our results and potential implications for adjustments to their clinic structure to improve TPT initiation and completion. Lastly, the continuation of adolescent and young adult studies remains of utmost importance to obtain greater clarity on variations in TB risk, TB regimen utilization, and TPT regimen preference to best serve the adolescent population.

Conclusion

This dissertation reported results on TB risk among non-U.S. born individuals in Washington state, TB prevention utilization and completion, and TB risk among YWHIV in Kenya (Chapters 2-4). Country of origin for non-US born individuals in the US provided a readily applicable risk evaluation when utilized among WHO incidence categories, which created more similar groups by incidence category (than by region of origin). The YWHIV in Kenya among our select clinics had low TPT utilization and high rates of TB incidence, especially among those who newly initiated ART. Age at clinic enrollment, perinatal infection, and duration on ART were all associated with increased TPT initiation and highlight the differences across the adolescent and young adult age group. Married status (compared to widowed, divorced, or cohabitating), presence of treatment supporter, and partner testing for HIV were associated with higher TPT initiation and/or lower TB disease risk; potentially highlighting the importance of interpersonal support as a protective factor for developing TB.

It is important to understand TB risk among non-U.S. born individuals and identify efforts to minimize this risk to attempt to achieve TB elimination in the U.S. Additionally, it is important to understand adolescent and young adult engagement with HIV care to adequately meet their needs and minimize TB transmission amongst this high-risk population. Integrated HIV/TB services offer an opportunity to access several resources; however, despite the current array of adolescent specific services (adolescent days, specific areas, and/or specific providers), adolescents and young adults may require additionally tailored services and support to ensure their engagement and retention. Through both ART and TPT, TB risk can be greatly diminished and advances in novel TPT regimens and TB diagnostics can be further leveraged. This dissertation work contributes to quantifying TB risk and evaluating prevention strategies across domestic and global communities. These results highlight opportunities to design public health approaches and changes to standard of care clinical practice to improve the health and wellbeing of overlooked populations like non-U.S. born individuals from high-risk TB countries in the U.S. and adolescents and young adults with HIV in Kenya.

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VITA

Danae Black completed her PhD in the Department of Epidemiology at the University of Washington in March 2023. Her research focuses on utilizing epidemiologic methods to gain deeper understanding of child and adolescent health, HIV, and tuberculosis burden, particularly among disadvantaged populations. Prior to completing her doctoral degree, she received her BS in Neuroscience from Texas Christian University and her MPH in Global Health Epidemiology from The George Washington University. Mrs. Black has been engaged in global health research in institutions including the University of Washington, the George Washington University, the Centers for Disease Control and Prevention, and Unitaid. Ms. Black has experience with data collection, analysis, and questionnaire development. She collaborates with recent colleagues in Nairobi, Kenya and previously worked with a diagnostic study based in Kisumu, Kenya. She utilizes strong epidemiological methods to develop research questions and utilize available data sources to fill research gaps in TB adolescent health research.