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Epidemiology of tuberculosis and hepatitis C virus (HCV) co-infection in the country of Georgia

By

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Doctor of Philosophy

Epidemiology

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Abstract

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Background: Tuberculosis and hepatitis C are major global public health problems. In addition to the burden that these two diseases pose separately, a substantial proportion of individuals are affected by both infections. However, there is a critical knowledge gap about how TB and HCV infection affect each other. The overarching goal of this dissertation was to characterize the epidemiology and impact of TB/HCV coinfection by analyzing nationwide data from the country of Georgia.

Methods: This dissertation included three studies to address knowledge gaps about the overlap of TB and HCV. In the first study, we compared the hepatitis C care cascade among patients with and without TB. The second study aimed to explore how hepatitis C affected the occurrence of TB and whether the incidence of TB was different among persons with treated and untreated hepatitis C. In the third study, we assessed the effect of HCV on TB recurrence and mortality in a cohort of patients successfully treated for TB.

Results: In the first study, we found that loss to follow-up from hepatitis C care was more common among patients with TB. Specifically, 20% of adult patients with TB and a positive HCV screening test did not undergo HCV confirmatory testing, and 43% of those with confirmed HCV did not start treatment for hepatitis C. The second study demonstrated that patients with hepatitis C, especially those with untreated infection, have a higher incidence of TB than those without HCV. The third study found that untreated HCV infection was associated with TB recurrence among patients with drug-susceptible TB. There was no association between HCV coinfection and mortality.

Conclusion: A more integrated approach is needed to manage patients with TB and HCV to reduce loss to follow-up from hepatitis C care, prevent active TB disease among hepatitis C patients, and improve long-term outcomes. This project was the first step in addressing the epidemiology and impact of overlap between hepatitis C and TB. It also provides multiple future opportunities to explore the other angles of this overlap.

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Chapter 1: Background

Introduction and Dissertation Aims

Both tuberculosis (TB) and hepatitis C virus (HCV) infection cause significant morbidity and mortality worldwide. Before the COVID-19 pandemic, TB was the leading infectious disease cause of death globally, resulting in an estimated 1.5 million deaths annually and 10 million new cases of active disease. Additionally, an estimated 1.7 billion people are latently infected with *Mycobacterium tuberculosis* (*Mtb,* the pathogen that causes TB) and at risk of developing active TB disease. Hepatitis C virus (HCV) infection is also a leading cause of infectious disease morbidity and mortality worldwide. In 2015, an estimated 71 million people were living with chronic HCV infection, and 400,000 died due to their HCV disease. Although both HCV and TB are common and, as preliminary data suggest, co-infection may lead to accelerated TB disease progression, their convergence and relationship have not been well described. Specifically, there is limited understanding about the impact of HCV infection on the risk of developing active TB and the impact of HCV co-infection on long-term outcomes, such as mortality or TB recurrence after TB treatment completion.

The Eastern European country of Georgia (population 3.7 million) has a high TB burden (incidence: 74 TB cases per 100,000 population in 2019). Further, chronic HCV infection is highly prevalent, affecting 5.4% of the general adult population, according to a 2015 estimate. In 2015, with support from the US Centers for Disease Control and Prevention (CDC) and other international partners, Georgia initiated the world's first nationwide

hepatitis C elimination program. The program provides free HCV testing and treatment for all citizens countrywide.

The overarching goal of this dissertation was to characterize the epidemiology and impact of TB/HCV co-infection by analyzing nationwide data from the country of Georgia. A high burden of both diseases, the world's first nationwide HCV elimination program, the existence of a National TB Program, and nationwide electronic databases make Georgia a unique setting to study the relationship of these two diseases of global importance. Better understanding the impact and consequences of TB/HCV co-infection could help optimize prevention and treatment strategies for both hepatitis C and TB control. This dissertation provides evidence to inform the inclusion of TB screening measures into hepatitis C care and identifies areas in the hepatitis C care cascade among patients with TB that need to be improved.

Specific aims of this dissertation are the following:

1. **To characterize the linkage to and retention in HCV care among patients with active TB disease who test positive on HCV antibodies**.

Hypothesis: The proportion of patients lost to follow-up in the HCV care cascade is higher among patients with TB than patients without TB.

2. **To evaluate whether HCV infection leads to higher rates of active TB disease**.

Hypothesis: Incidence of TB is highest among those with untreated HCV infection, followed by those cured of HCV, and those free of HCV with the lowest incidence.

3. **To assess the effect of HCV co-infection on long-term outcomes among patients successfully treated for TB.**

a. **To assess the effect of HCV co-infection on all-cause mortality among patients successfully treated for TB**

b. **To assess the effect of HCV co-infection on TB recurrence among patients successfully treated for TB**

Hypothesis: Mortality and TB relapse rates after TB treatment completion are higher among patients with TB/HCV co-infection than those with only TB disease.

The dissertation is organized in the following manner: the rest of chapter 1 includes an extensive literature review about the epidemiology of tuberculosis, hepatitis C and their overlap, and describes the sources of data used. Chapters 2, 3 and 4 contain the manuscripts corresponding to each of the specific aims above. Chapter 5 provides overall conclusions, strengths, limitations and implications of this dissertation.

Epidemiology of tuberculosis

Global burden and pathogenesis of tuberculosis

Tuberculosis (TB) is one of the leading infectious disease-related causes of death globally. In 2019, an estimated 10 million people developed active TB disease, and there were 1.2 million TB deaths among HIV-negative people and 208,000 deaths among people living with HIV infection (PLHIV).[1] TB disease occurs throughout the world but primarily affects persons in low- and middle-income countries. Starting from the middle of the 20th century, TB incidence steadily declined globally due to the development of effective anti-TB medications.[2] However, TB re-emerged as a major public health problem in the 1980s and 1990s. For most parts of the world, this re-emergence was largely driven by the HIV

epidemic, given that PLHIV are at higher risk of TB than healthy individuals.[2-4] In some countries, TB has re-emerged due to socio-political unrest and instability. As an example and relevant to this dissertation, post-soviet countries experienced disruption of essential healthcare systems after the collapse of the Soviet Union.[5] This led to increased TB incidence in the early 1990s even in low HIV burden countries, including Georgia.[5]

The causative agent of TB is *Mycobacterium tuberculosis* (*Mtb*), which is transmitted via airborne droplet nuclei and predominantly affects the lungs but can cause disease of any organ.[6,7] After entering a human host, *Mtb* may cause active TB disease or latent TB infection (LTBI). In contrast to active TB disease, LTBI is not accompanied by any clinical or radiological manifestations but can progress to active TB disease due to reactivation of *Mtb*.[4] The overall estimated risk of reactivation is 5-10% during the lifetime.[8] Globally, an estimated 1.7 billion people have LTBI and thus are at risk of developing active TB. This is a massive reservoir for active TB disease, and TB control cannot be achieved without LTBI treatment.[9] Risk factors for progression from LTBI to active disease include HIV infection, diabetes, smoking, and organ transplantation, among others.[10]

Treatment regimens are available for LTBI to prevent progression to active TB, with efficacy ranging from 60% to 90%.[11] LTBI treatment policies vary by country and depend on the burden of TB and HIV, and available resources.[12] Unlike low-burden, high-income countries, LTBI treatment is uncommonly used in low-income, high-burden countries.[13] However, according to the most recent World Health Organization (WHO) guidelines, contacts of TB cases may be given treatment even in countries with a high TB incidence.[14,15] Therefore, diagnosing and treating people with LTBI can contribute to improved TB control by preventing active TB disease and reducing TB disease incidence.

TB control is challenging for various reasons. One of them is that identifying and treating people with active TB is suboptimal, with only 7 million of an estimated 10 million TB cases notified in 2018.[16] This gap is explained by both underdiagnosis and underreporting. Acknowledging the lack of adequate diagnosis and treatment of TB, in 2014 the WHO initiated an End TB Strategy, which called for integrated, patient-centered care and systematic screening of contacts and high-risk groups.[17] Groups with a high risk of active TB disease include smokers, people living with HIV, and people with diabetes mellitus, among others.[16,18-21] Relevant to aim 2 of this dissertation, some studies suggest that those with chronic hepatitis C virus (HCV) infection are also at higher risk of tuberculosis,[22]. However, compelling evidence is lacking due to limited data. Therefore, active TB screening or preventive measures are usually not undertaken among patients diagnosed with chronic HCV.

TB treatment – regimens and complications

Specific treatment for tuberculosis exists, but treatment options, duration, and success rate varies between drug-susceptible (DS) and drug-resistant (DR) forms of tuberculosis. According to WHO definitions, treatment outcomes are classified into treatment success (cured or completed treatment), failed treatment, death, and loss to follow-up.[23] Two of the most important first-line drugs used for DS TB treatment are isoniazid and rifampicin.[24] Treatment duration for DS TB is usually six months.[25] Globally, the treatment success rate among DS TB patients is 85%.[1]

Drug-resistant TB (DR TB) remains a major public health threat. In 2018, there were about half a million new cases of TB resistant to rifampicin. Among these rifampicin-

resistant (RR-TB) cases, 78% of patients had multidrug-resistant TB (MDR TB), meaning that bacteria were also resistant to isoniazid.[16] These drug-resistant forms of TB have limited treatment options that are more toxic, longer in duration, and are associated with lower treatment success and higher mortality than DS TB strains.[26,27] Globally, the treatment success rate among MDR and RR TB patients was only 57% in 2019.[1] *Mtb* can also be resistant to some of the second-line drugs – a condition called extensively drug-resistant TB (XDR TB), which is characterized by even lower treatment success rate (39%).[16,28,29]

Treatment for both drug-susceptible and drug-resistant forms of TB is associated with frequent and sometimes severe adverse events which might necessitate discontinuation of a drug.[30-32] In a recent meta-analysis, it was found that 23.5% of MDR TB patients had at least one drug permanently stopped due to an adverse event.[33] Adverse events range from mild gastrointestinal symptoms to more severe conditions, such as hepatotoxicity, ototoxicity, nephrotoxicity, and peripheral neuropathy. Drug-induced hepatotoxicity or liver injury is a major adverse event that occurs in 5 to 33% of patients. It may result in severe forms of liver inflammation, liver failure, and death.[34] Isoniazid is the most common drug associated with hepatotoxicity, but rifampicin and pyrazinamide are also known to cause it.[33-35] Studies have found that that drug-induced hepatotoxicity during TB treatment occurs more frequently in patients co-infected with HCV (more details in section 1.4.3).[36-38]

Cured or not cured? Recurrence after TB treatment

One of the challenges in TB control is a recurrence of TB after treatment completion, which requires retreatment of a patient.[39] Recurrence is a repeat occurrence of TB disease (second or subsequent episode) in a patient previously treated for TB. Rates and reasons of recurrence vary widely between countries. One review reported that the proportion of recurrent cases ranges from 4.9% to 47%.[39] Factors most commonly associated with TB recurrence include HIV, malnutrition, diabetes, renal and liver failure, and substance abuse.[40] All of these are immunosuppressive conditions, which highlights the critical role of immune suppression in recurrence.[39] Therefore, other factors, such as HCV coinfection, that disrupt the immune response against *Mtb* may also increase the risk of TB recurrence.

Recurrence can occur via two mechanisms: (1) Endogenous relapse, i.e., repeated episode of TB caused by regrowth of the same strain of *Mtb* that caused the initial episode, or (2) Exogenous reinfection with a new *Mtb* strain.[39,41] Relapse more commonly presents earlier after treatment completion, while reinfection is more prevalent among cases recurring after one year from treatment completion.[42,43] Distinguishing relapse from reinfection is challenging and requires genotypic analysis to determine whether the recurrent episode of TB was caused by the same or a new strain of bacteria.[41] However, genotyping is usually not routinely performed in recurrent cases.

Recurrence occurs about twice as frequently after incomplete TB treatment as after completed treatment, but the recurrence rate is still high even among patients who successfully completed TB treatment. Some studies in high TB incidence settings report 9% to 14% of patients developing recurrence within 2-5 years after successful completion

of treatment.[44,45] A review of 32 studies found that the overall recurrence rate was 3010 per 100,000 person-years at six months after successful treatment completion and was almost five times greater in high vs. low TB incidence countries.[46] In low TB incidence settings, recurrence is usually primarily driven by relapse, while reinfection is more common in high TB incidence countries.[39,42,47,48] However, genotypic analysis of 32 MDR patients with TB recurrence in the country of Georgia (high TB burden setting) found that 25 (83%) of these cases were due to relapse.[49]

Mortality after TB treatment

Even in the absence of TB recurrence, mortality is higher among those previously diagnosed with and treated for TB disease compared with those without a history of TB. Deaths from TB estimated by the WHO (1.5 million in 2018) includes the people with TB who die before or during TB treatment but do not consider deaths after TB treatment.[23] However, people treated for TB have long-term health impairment. Studies suggest that patients treated for TB have 3-4 times higher mortality compared to the general population.[50,51] Death is caused by both pulmonary and extrapulmonary sequalae of TB, such as lung impairment and cardiovascular complications.[50-54] A study from Israel reports that liver diseases rank higher among reasons of death in patients cured of TB compared to the general population.[51] However, more thorough evidence about the role of hepatitis C and liver disease in post-TB mortality is needed. The potential role of HCV infection in post-TB mortality is discussed in section 1.4.3.

Epidemiology of TB in the country of Georgia

The Eastern European country of Georgia (population 3.7 million) has a high TB burden and is designated as a high-priority country for TB control in the WHO European Region.[16,55] After the fall of the Soviet Union in 1991, TB incidence in Georgia increased from 8,000 diagnosed cases in 1991 to more than 14,000 in 1994, before starting to decline gradually.[19,56] Incidence of TB has continued to decline in the following decades and reached 2,590 notified cases in 2018, with an estimated incidence of 74 cases per 100,000 population.[16,57] This decline was achieved by providing universal access to testing and treatment countrywide starting from the late 2000s. All diagnostic and treatment procedures (including medications) for both drug-susceptible and drug-resistant TB are provided free of charge within the Georgian National TB Program (NTP).

Despite success in decreasing the incidence and providing universal access to TB diagnosis and treatment, several major challenges remain to TB control in Georgia. These include diagnostic delay, high prevalence of drug-resistant TB, and a high rate of unfavorable treatment outcomes among MDR and XDR cases.[58-61] In 2019, 12% of new and 32% of retreatment TB cases were MDR or RR.[1] Treatment success rates in the most recent cohorts are 84% among DS TB patients, 64% among MDR and RR cases, and 60% among XDR cases. Furthermore, mortality is high among XDR TB patients and those lost to follow-up during MDR or XDR treatment.[58,59,62] However, post-treatment mortality among all TB patients in Georgia has not been previously evaluated.

Epidemiology of hepatitis C

Morbidity, mortality, and pathogenesis of HCV

Hepatitis C is a viral infection caused by the hepatitis C virus (HCV). HCV is one of the five viruses causing viral hepatitis, the others being hepatitis A, B, D, and E viruses.[63-66] Collectively, viral hepatitis caused an estimated 1.34 million deaths in 2015, with 96% of mortality caused by hepatitis B and C infections.[63] A vaccine against hepatitis B is available and has been successfully implemented in many countries, while a vaccine against hepatitis C has not been developed.[67] In 2015, 71 million people were living with chronic hepatitis C globally, and an estimated 400,000 people died due to infection. The same year, 1.75 million new cases of HCV infection occurred worldwide.[63] The HCV epidemic affects all parts of the world, with the highest prevalence in Eastern Mediterranean and European regions.[63] With recent successes in the availability of effective treatment options, the WHO encourages countries to scale up testing and treatment of HCV to eliminate viral hepatitis as a major public health threat by 2030.[68]

HCV can be detected in blood and other body fluids, such as saliva and semen, but transmission mainly occurs via infected blood or blood products.[69-74] In high-income countries, needle-sharing for injection drug use (IDU) is the most common transmission mode.[70,75,76] However, healthcare-related transmission, such as unsafe injections and transfusion of infected blood, also contributes to a substantial proportion of transmissions, especially in low- and middle-income countries where infection prevention and control practices are suboptimal.[70,75,77,78] Other potential routes of transmission include perinatal transmission from mother to child, and sexual transmission, primarily among HIV-positive men who have sex with men[79-81] In some

countries, community exposures, such as barbering, tattooing and piercing have also been reported as risk factors for HCV infection. [82-85]

After the initial infection, HCV causes acute illness, which is mild and often unrecognized.[86,87] Eighteen to 34% of infected individuals spontaneously clear the virus, while in the rest, the infection progresses and persists as chronic hepatitis C.[87,88] The majority of persons chronically infected with hepatitis C remain unaware of their infection because it progresses slowly and might not cause any clinically apparent manifestations for many years.[89-91] However, persistent liver inflammation leads to cirrhosis in approximately 10–20% of patients over 20–30 years.[87] Cirrhosis might remain stable in some proportion of patients but cause severe complications in others: patients with cirrhosis have a 1-5% annual risk of hepatocellular carcinoma (HCC) and 3-6% annual risk of liver decompensation. After an episode of decompensation, there is a 15-20% risk of death during the following year.[87] Globally, 27% of cirrhosis cases and 25% of HCC cases are attributable to HCV.[92] Risk factors for progression of liver fibrosis to cirrhosis, HCC, and decompensation include HIV coinfection, alcohol use, diabetes, and older age.[93-95]

HCV diagnosis and treatment

Even though people with chronic HCV infection may not experience any clinical symptoms for decades, evidence of HCV infection can be detected via laboratory tests several weeks after the initial infection.[96] These tests can be grouped into two broad categories – screening and confirmatory tests. Screening tests are usually aimed at detecting anti-HCV antibodies and include both rapid tests and laboratory-based tests.[97]

Individuals who spontaneously clear the virus after initial exposure might have HCV antibodies for the duration of their lifetime, so a positive anti-HCV antibody test by itself is not indicative of chronic infection.[98] Confirmatory viremia tests aim to determine active infection and include plasma HCV RNA PCR tests and HCV core antigen tests.[97,99] HCV testing coverage is very low globally. In 2015, It was estimated that only 20% of people with HCV infection had been tested and knew their status.[63] However, in recent years, many countries have scaled up their public health programs to identify more people with HCV infection.[100] After HCV testing, further linkage to care and treatment initiation is still a challenge due to the high cost of diagnostics and direct-acting antiviral (DAA) medications in most parts of the world.[101]

There is no currently available HCV vaccine which makes HCV elimination a challenge. However, the global HCV epidemic can be controlled and elimination achieved with strategies that include highly effective treatment options.[100-102] In recent years, there has been remarkable improvements in treatment options, with the emergence of newer simplified DAA regimens.[103] One of the first DAAs was sofosbuvir, followed by sofosbuvir in combination with ledipasvir and velpatasvir, among others.[104] The treatment course of DAAs ranges from 8 weeks to 24 weeks, depending on the severity of liver damage, virus genotype, and medication used.[105] Adverse reactions during sofosbuvir-based regimens are usually mild and include headache, fatigue and anemia, seen in 10-20% of patients.[106,107] Approximately 1-2% of patients may develop severe adverse reactions which might require treatment discontinuation.[107,108] A patient is considered cured of hepatitis C if RNA testing after at least 12 weeks of treatment completion demonstrates a sustained virologic response (SVR), i.e., no detectable virus.[104] The cure rates with

combination DAA-based therapies, such as sofosbuvir/ledipasvir, is approximately 95%, and reaches 99% in some settings[109,110].

HCV in Georgia

Chronic HCV infection is highly prevalent in Georgia, affecting 5.4% of the general adult population (~150,000 individuals) based on 2015 prevalence estimates – the highest prevalence among Eastern Europe and Central Asia countries and among the ten countries with the highest prevalence worldwide.[90,111,112] In 2015, with support from the US CDC and other international partners, Georgia initiated the world's first nationwide hepatitis C elimination program, which provides free HCV testing and treatment for all citizens.[113-115] Hepatitis C screening through antibody testing was integrated into multiple existing programs and settings, such as blood safety, antenatal surveillance, harm reduction, inpatient settings, national TB and HIV programs, and prisons.[114,116-119] In 2019, there were approximately 1,400 medical facilities providing initial HCV screening using antibody tests and 41 clinics providing diagnostic and treatment services countrywide (unpublished data from the National Center for Disease Control and Public Health). Georgia has been named as the world's first Center of Excellence in HCV Elimination by the European Association for the Study of the Liver (EASL) - International Liver Foundation, and is considered as one of the few countries on track to achieve HCV elimination by 2030.[100,101,114,120]

Despite successes in scaling up hepatitis C testing and treatment, identifying people with HCV infection and linking them to treatment remains a challenge. By April 2020, there were approximately 21,000 people lost to follow-up after a positive screening test result,

i.e., they did not undergo further confirmation using RNA or core antigen testing. HCV infection was confirmed in 86,502 individuals, i.e., ~58% of the estimated total number of people living with chronic HCV infection in Georgia.[90] Among those, only 80% initiated the treatment (Figure 1). Georgia has tried to remove barriers and improve linkage to care by integrating screening, care, and treatment services into primary healthcare settings and harm-reduction network organizations countrywide.[114]

Figure 1.1. Georgia Hepatitis C Elimination Program Care Cascade, April 28, 2015 – April 30, 2020

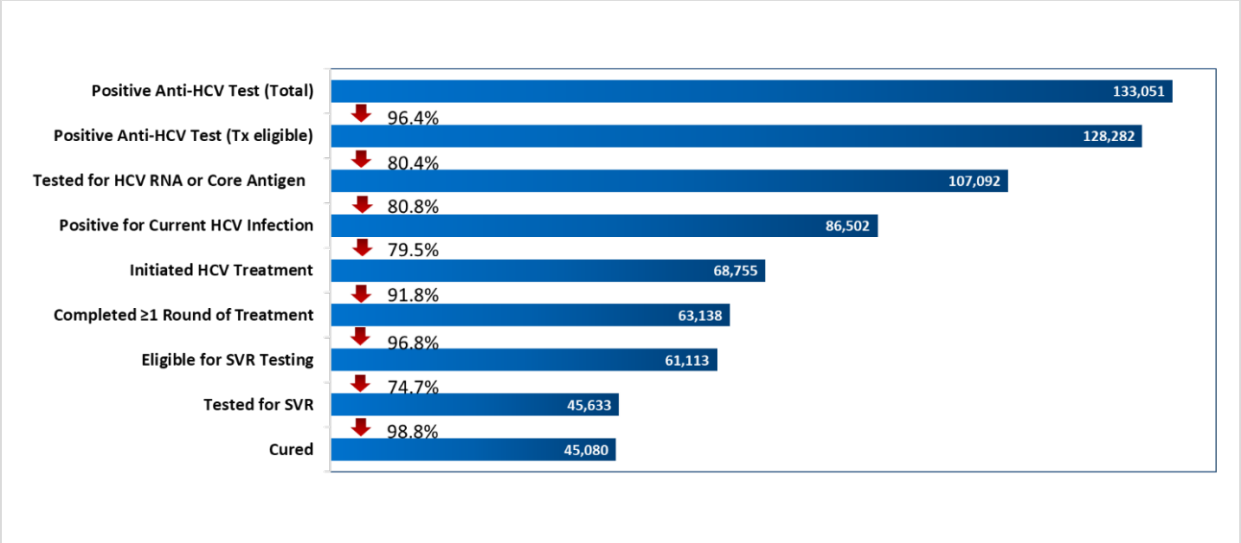

Figure source: HCV elimination program monitoring and evaluation team, CDC.

TB/HCV coinfection

Epidemiologic overlap between TB and HCV

TB is an airborne bacterial disease predominantly affecting the lungs, while hepatitis C is a blood-borne viral infection affecting the liver. Despite stark differences, there are many social and biological pathways through which these two diseases intersect. In this and the following sections, we will describe both documented and hypothesized mechanisms of the bidirectional relationship between TB and HCV infection and identify critical gaps in knowledge, some of which will be addressed in the subsequent chapters of this dissertation.

There are several population subgroups in which both TB and HCV infection are more common compared to the general population, such as homeless or incarcerated individuals and people who inject drugs (PWID).[121-123] According to a 2014 estimate, globally, 15.1% of incarcerated people had HCV infection and 2.8% had active tuberculosis.[124] Injection drug use is a strong risk factor for HCV infection, with 6.1 million people with recent injection drug use living with HCV infection, corresponding to 8.5% of all HCV infections globally.[125] It is also reported that PWID have a higher prevalence of LTBI and incidence of active TB disease.[126-128]

Epidemiologic data describing persons affected by both TB and HCV is relatively scarce. Available evidence suggests that the overlap between these two diseases varies by country. A meta-analysis of 21 studies reported that the overall prevalence of HCV infection among patients with active TB was 9%. Results varied widely between countries and ranged from 2 to 27%.[129] The meta-analysis combined prevalence estimates of both HCV antibody tests and PCR tests, so more accurate global estimates about the prevalence of active HCV

infection among TB patients are not available. It is also unknown what proportion of patients with TB affected by HCV infection are linked to hepatitis C care to initiate treatment and achieve SVR. We will study this issue in the Georgian context in Chapter 2 of this dissertation.

Another aspect of TB/HCV overlap, which is of high importance but not well studied, is whether HCV infection increases the risk of TB disease. A cohort study from Taiwan found that people diagnosed with hepatitis C have a 1.5-times higher incidence rate of TB, but the association was even stronger after adjusting for potential confounders, with an adjusted hazards ratio (aHR) of 3.20 (95% CI, 1.85–5.53), suggesting a causal effect of HCV on the occurrence of TB.[22] However, the study did not differentiate between treated and untreated HCV infection. Additionally, it is estimated that people with cirrhosis have a higher risk of TB, even after adjusting for HCV status (aHR=3.55, 95% CI: 3.08, 4.09).[130] A case-control study from the US also reported that people with HCV infection have an almost 3-times higher prevalence of TB, although we cannot draw causal conclusions from this study.[131] In chapter 3 of this dissertation, we will address whether HCV infection leads to a higher rate of tuberculosis in the largest cohort described to date.

Immunologic intersections of HCV infection and TB

In addition to the overlap of TB and HCV infection on a population level (described in the previous section), the two pathogens interact on a biologic level, highlighting the biologic plausibility of HCV affecting risk of TB incidence, relapse, and death. HCV suppresses various components of the immune system. It reduces the number of CD4 T lymphocytes, which might have an overall negative effect on the immune response against *Mtb*.[132]

Immune profiles of individuals with TB or HCV have been studied separately, but evidence regarding the immunology of HCV/TB co-infection is very limited. A recent study comparing immunologic profiles of patients with only TB and those with both TB and HCV found significant differences in the expression of several immune markers. In patients with both diseases, interferon-gamma (IFN-γ), CD38 and HLA-DR receptors, which are markers of CD4 T-cell activation, were lower. Levels of interleukin-10 (IL-10), which is a cytokine responsible for downregulation and inhibition of immune response,[133] were higher in patients with both TB and hepatitis C, compared to patients with only TB.[134] Exploring specific immune pathways responsible for TB control and immune reactions to HCV infection shows that there are at least four mechanisms by which HCV could interfere in immune control of TB.

1. After entry into the host organism, *Mtb* bacilli are captured by macrophages, one of the key cells in the innate immune response. Macrophages might effectively eliminate the bacteria or contain them without complete elimination, resulting in the persistence of bacilli within macrophages, developing granulomas leading to LTBI. One of the most important immune mechanisms that activate macrophages to destroy or contain Mtb bacilli effectively are mediated by cytokines IFN-γ and tumor necrosis factor α (TNF-α).[135,136] HCV infection has a strong effect on interferon production. At the initial infection by HCV, IFN-γ production is increased, but if the virus is not spontaneously cleared and infection progresses to the chronic condition, IFN-γ levels decrease and remain low through the course of infection.[137] Therefore, chronic HCV infection might hinder the IFN-γ-mediated activation of macrophages which is essential for *Mtb* control.

2. HCV infection induces the production of type 1 interferons (IFN-α and IFN-β), which have a crucial role in controlling many viral infections.[137] However, unlike with viruses, type 1 interferons in high and sustained levels have been found to harm the response against bacterial infections, including *Mtb,* by inducing inhibitory cytokine IL10 and inhibiting protective cytokines, such as IL-12, IFN-γ, and TNF-α.[138] Therefore, chronic HCV infection, associated with prolonged high and sustained levels of type 1 IFNs, can negatively affect the immune response towards both new infections with *Mtb* and existing LTBI.

3. Natural Killer (NK) cells are increasingly recognized as important actors in the immune response against *Mtb*.[139] Progression to active TB disease is preceded by a decline in the number of circulating NK cells.[140] NK cells have direct cytotoxic activity against bacteria and indirect effects via activation of different cells by releasing IFN-γ and TNF-α. HCV infection negatively affects NK cell population diversity, and IFN-γ and TNF-α production by NK cells is significantly lower in HCV-positive patients than in healthy individuals.[141,142] Therefore, dysfunction of NK cell activity by HCV infection can also contribute to the progression of active TB disease.

4. One of the mechanisms for direct destruction of *Mtb* involves the release of cytotoxic substances, perforin and granulysin, by several types of lymphocytes, including CD8 T cells.[135] Viral persistence can cause the development of functionally inferior T cells – a condition referred to as T-cell exhaustion.[143,144] T-cell exhaustion has been described during multiple viral infections, including chronic HCV infection.[145-147] T-cell exhaustion can affect the ability of CD8 T cells to produce and release adequate amounts of

substances, including IFN-γ and perforin, negatively affecting one more mechanism of the immune response against *Mtb*.[135]

The mechanisms, as mentioned above, are an incomplete list of either recognized or hypothesized plausible immune pathways in which *Mtb* and HCV intersect. However, they demonstrate the ability of HCV to impact a human host's immune response aimed to eliminate or effectively contain the bacteria. Therefore, these mechanisms demonstrate the biological plausibility of the hypothesis that HCV infection can increase the risk of developing active TB disease through primary progression or relapse after seemingly successful treatment.

Clinical implications of TB/HCV coinfection

In addition to the effect of HCV on the progression or relapse of active TB disease, the overlap of these two diseases has significant implications for the clinical management of a patient once both diseases are already present. One of the main issues in managing persons with TB and HCV co-infection is drug-drug interactions, precluding the concomitant use of some of the first-line anti-TB and antiviral medications.[148] Several drug-drug interactions between TB and HCV drugs are observed, and others have not yet been identified in studies but are hypothesized based on the pharmacokinetic features of these drugs. Specifically, the issue of interaction is mainly related to first-line TB drugs rifamycins and, to a lesser extent, isoniazid, which are metabolized in the liver.[148-150] It was found that daily use of rifampicin (one of the rifamycins) decreases the concentration of the most widely used anti-HCV DAAs - sofosbuvir, ledipasvir and velpatasvir.[151,152] Due to

these concerns, concurrent treatment of drug-susceptible TB and HCV is contraindicated, and hepatitis C treatment is initiated only after TB treatment completion.[105,153]

Considering their pharmacokinetic properties, TB drugs used for second-line treatment lack clinically significant interactions with HCV drugs and could, in theory, be used in parallel to DAAs. However, this approach has only been used on individual cases and is not thoroughly studied.[148,154] Most DR TB patients, similar to DS TB patients, are not concurrently treated even when there are no apparent drug-drug interaction concerns, and hepatitis C treatment is postponed until TB treatment completion.

Another issue that might be exacerbated in coinfected patients is drug-induced hepatotoxicity. New DAA drugs for HCV treatment have a good safety profile and only sporadic cases of liver toxicity have been reported.[155] Liver toxicity related to new DAAs specifically among patients previously treated for TB has not been studied extensively, and there have only been case reports.[156] However, hepatotoxicity of anti-TB drugs is of serious concern in general and especially among patients with HCV coinfection, who are at approximately 3-times higher risk of drug-induced hepatotoxicity, compared to HCV-negative patients with TB.[36,38] This combined effect of TB drugs and HCV can cause long-term impairment of liver function and could be one of the factors explaining high mortality after TB treatment.[51] The effect of HCV on mortality after TB treatment has not been previously studied, and we tried to address this gap of knowledge in chapter 4 of this dissertation.

Data sources for dissertation

TB surveillance database

The TB surveillance database is managed by the Georgian National Center for Tuberculosis and Lung Disease (NCTLD). It includes clinical and TB treatment-related information on every patient enrolled in the National TB Program (NTP) of Georgia. The NTP provides free-of-charge diagnosis and treatment for TB countrywide (on average 2,300 new cases enrolled annually in 2015-2018). The database was provided for this project on September 30, 2020 by the data managers at NCTLD and included records on diagnosed TB cases from January 1, 2015, up to the date of data provision. It was cross-checked with the national death registry by the data management team at NCDC, using the unique national ID number. If a person was found to be deceased, date of death was extracted. Variables in the NCTLD database that were available for this dissertation project included:

Identifier: Person Code (unique patient identifier, derived from encrypted, unique national identifying number)

Socio-demographic variables: Sex, age, month and year of birth, region of residence, medical facility name, employment status, internal displacement status (whether a patient is from Georgian conflict regions occupied by Russia), history of imprisonment.

TB diagnostic and treatment variables: TB diagnosis date, sputum microscopy result, treatment start date, Xpert MTB/RIF result, culture analysis result, DST result, whether a case is new or previously treated (treatment after relapse, failure, or loss to follow-up), treatment outcome, outcome date, HCV antibody test result, HIV test result.

National HCV screening registry

The national HCV screening registry is a real-time, nationwide web-based system managed by the NCDC. The screening registry collects data from all stakeholders providing hepatitis C screening through antibody testing throughout the country. These stakeholders include blood banks, antenatal care clinics, hospitals, outpatient clinics, non-governmental organizations providing harm-reduction services, and NCDC with its regional laboratory network. As of January 5, 2020, 1,444 stakeholders have entered screening data into the registry. An identifier used during data entry is the national ID number, which is cross-checked with the civil registry database and demographic information is automatically extracted from the latter. This process ensures the accuracy of recorded national ID numbers and basic demographic information.

NCDC's data management team extracts the data for a routine HCV hepatitis C care cascade analysis each month. The database is cross-checked with the national death registry using the unique national ID number, and if a person is found to be deceased, the date of death is extracted. Data from the registry are then linked to the HCV clinical database (ElimC below). Data analysis is performed by CDC's HCV elimination program monitoring and evaluation team (CDC Tbilisi office and CDC Division of Viral Hepatitis, Atlanta, GA, USA).

The registry includes demographic data and anti-HCV antibody results. The variables from the screening registry available for this dissertation project include:

Identifier: Person Code (unique patient identifier, derived from encrypted, unique national identifying number)

Socio-demographic variables: Sex, age, month and year of birth, place of residence (region, district, municipality)

Hepatitis C testing variables: testing material, testing method, testing date, test result, name and location of organization performing testing.

ElimC (HCV clinical database)

The hepatitis C Elimination Program clinical database, called "Elimination C" (ElimC) is owned by the Georgian Ministry of Health and is managed by NCDC. ElimC is a nationwide web-based database that collects information from all 41 clinics providing HCV diagnostic and treatment services to patients enrolled in the HCV elimination program. ElimC includes every individual who underwent confirmatory testing after positive HCV screening in the HCV elimination program. If confirmatory testing was positive, other diagnostic test results and treatment-related information are also entered in ElimC. Data is entered into the ElimC system directly by the clinics. An identifier used during data entry is the national ID number, which is cross-checked with the civil registry database, and demographic information is automatically extracted from the latter. This process ensures the accuracy of recorded national ID numbers and basic demographic information.

Similar to the HCV screening registry, NCDC's data management team extracts the data from ElimC for a routine HCV care cascade analysis each month. The database is cross-checked with the national death registry using a unique national ID number, and if a person is found to be deceased, the date of death is extracted. Data from ElimC is then linked to the HCV screening registry. Data analysis is performed by CDC's HCV

elimination program monitoring and evaluation team (CDC Tbilisi office and CDC Division of Viral Hepatitis, Atlanta, GA, USA). Variables of ElimC that are available for this dissertation project include:

Identifier: Person Code (unique patient identifier, derived from encrypted, unique national identifying number)

Socio-demographic variables: Sex, age, month and year of birth, place of residence (region, city),

HCV diagnostics: HCV confirmatory testing date, result, and name of the facility performing testing;

If HCV is confirmed and the patient enrolls in the elimination program, the following variables are available: Genotype test result and date; medical facility; liver fibrosis (FIB4 score, fibroscan); liver function tests (ALT, AST, Bilirubin, creatinine); hepatitis B surface antigen (HBsAG) test date and result; date of treatment initiation; treatment side effects; drug regimen; treatment duration; RNA test result (weeks 4, 12, 16, 20, 24, 48); Sustained virologic response (SVR) after 12 weeks of treatment completion;

Summary

Globally, TB has been the leading infectious disease-related cause of death for the past six years until the COVID-19 pandemic, resulting in more deaths annually than any other single infectious disease, including HIV. Similarly, HCV also infects millions of people every year and is associated with substantial morbidity and mortality. Even though both

infectious diseases share many behavioral and social risk factors, there is a critical gap of knowledge about how they affect each other. For example, it is not well studied if patients with TB/HCV coinfection are less likely to initiate treatment for HCV infection due to treatment fatigue, as is the case for TB/HIV coinfection. On the other hand, it is not thoroughly explored if HCV causes an increased risk of TB disease, relapse after TB treatment, or death due to immune suppression and liver damage that it causes. The country of Georgia, with its nationwide Hepatitis C Elimination Program and National TB Program, provides unique opportunities to address these gaps of knowledge regarding TB/HCV coinfection. In this dissertation, we explored some of these gaps in knowledge and generated evidence that will help national TB and hepatitis C control programs make evidence-based decisions aimed at early detection and better management of these diseases.

Chapter 2: Hepatitis C cascade of care among patients with and without tuberculosis

Abstract

Background: Georgia initiated a nationwide hepatitis C virus (HCV) elimination program in 2015 to address the high burden of infection. HCV screening was integrated into multiple existing programs, including the National Tuberculosis Program (NTP). We sought to compare loss to follow-up (LFU) from different steps of the hepatitis C care cascade among persons diagnosed with active TB disease to those without the diagnosis of TB.

Methods: We merged databases from the HCV elimination program, NTP, and national death registry for 2015-2020 using national ID numbers. We estimated the proportion of patients with and without TB who were LFU at each step of the HCV care cascade and explored temporal changes in these proportions.

Results: Among 11,985 patients with active TB, 9,065 (76%) were screened for HCV antibodies and 1,665 (18%) had a positive result; 108 patients (6%) died before viremia testing could be performed. Of the remaining 1,557 patients, 1241 (80%) patients underwent viremia testing and 1,025 (83%) had positive viremia results, of which 443 (43%) were LFU without initiating HCV treatment. Overall, among patients with confirmed active HCV infection, only 28% of patients with TB had a documented cure from HCV, compared to 55% among patients without TB. LFU after positive antibody testing substantially decreased in the last three years, from 32% among patients diagnosed with TB in 2017 to 12% among those diagnosed in 2019. LFU after positive

viremia testing increased by year, from 21% among patients diagnosed with TB in 2015 to 56% among those diagnosed in 2019.

Conclusions: LFU from hepatitis C care after a positive antibody or viremia test is more common among patients with TB compared to those without. Existing large-scale programs for both TB and HCV in Georgia create a unique opportunity for integrated care of these two diseases that could potentially reduce the loss to follow-up and improve patient outcomes.

Introduction

Both tuberculosis (TB) and hepatitis C virus (HCV) infection cause substantial morbidity and mortality worldwide. Before the COVID-19 pandemic, in 2019, there were an estimated 10 million new cases of active TB globally, resulting in an estimated 1.4 million deaths, the leading infectious disease cause of death in the world.[1] In 2019, an estimated 58 million people were living with chronic HCV infection and 290,000 died as a result of their HCV disease.[157,158] TB and HCV infection are often concentrated in the same high-risk population subgroups, such as homeless or incarcerated individuals and people who inject drugs (PWID).[121-123] However, the relationship of these two infectious diseases has not been well described. Specifically, it has not been well described if patients with current or past TB disease receive hepatitis C care as completely and in a timely manner as the general population.

Hepatitis C diagnosis, treatment, and assessment of cure consist of multiple consecutive steps, collectively known as the hepatitis C cascade of care.[159] The cascade starts with hepatitis C antibody screening and ends with the determination of cure based on sustained virologic response (SVR) at 12 weeks after treatment completion.[96-103,105,160] Available data has found that loss to follow-up (LFU) at different stages of the hepatitis C cascade of care is common.[161] In 2017, globally, only one in five people living with hepatitis C had been tested and knew their status, and only about 38% of people with a known diagnosis were treated.[63,158,162] LFU from hepatitis C care among patients with both TB and hepatitis C has not been previously studied. However, linkage to care and treatment for HCV infection might be even more urgent for patients treated for TB compared to those without TB. Drug-induced liver toxicity of anti-TB drugs is one of the most serious side effects of TB treatment, and patients with HCV coinfection are at approximately 3-

times higher risk of this complication compared to HCV-negative patients with TB.[36,38] Joint effect of TB drugs and HCV infection can cause long-term impairment of liver function, making timely management of hepatitis C a priority in this group.

The Eastern European country of Georgia (population 3.7 million) is designated as a high-priority country for TB control in the WHO European Region, with an incidence of 74 TB cases per 100,000 population in 2019 and a high burden of Multidrug-resistant (MDR) TB.[1,55] Chronic hepatitis C is also highly prevalent in Georgia, affecting an estimated 5.4% of the general adult population (~150,000 individuals) based on a 2015 serosurvey – the highest prevalence among countries of Eastern Europe and Central Asia.[90,111] Historically, there has been a substantial overlap in the population affected with these two infectious diseases in Georgia, with previous studies reporting >20% of newly diagnosed active TB cases having HCV antibodies, indicative of current or past infection.[36,163]

To address the high burden of HCV infection, Georgia initiated the first nationwide hepatitis C elimination program in 2015, including free hepatitis C testing and treatment for all citizens.[113-115] The cost of confirmatory viremia testing was initially fully covered by the government only for persons with low income but became freely available for everyone beginning in March 2018.[116] Free hepatitis C screening through antibody testing was gradually integrated into multiple existing programs and settings, including the National TB Program (NTP), which provides diagnostic and treatment services for TB countrywide.[114,116-119] Before 2018, HCV antibody testing was performed routinely among patients with MDR TB and sporadically (by indication) among patients with drug-susceptible (DS) TB. According to the new TB treatment guideline in Georgia adopted in July 2018, all patients newly diagnosed with TB are recommended to be routinely screened for HCV antibodies. If an antibody test is positive, blood samples are sent to the

National Center for Disease Control and Public Health (NCDC) for HCV viremia testing. However, there is no formal referral system in place linking patients with TB to hepatitis C care, and it is unknown how many patients with TB and chronic hepatitis C infection go on to receive hepatitis C treatment. In-depth analyses of the hepatitis C care cascade among patients with TB have not been conducted to date.

The objectives of this study were to (1) to compare the hepatitis C cascade of care among patients who were diagnosed with TB in Georgia between 2015-2019 and persons without TB; (2) to identify factors associated with LFU in hepatitis C care among patients with TB. Findings from this analysis will be a valuable contribution to the Georgian Hepatitis C Elimination Program and other similar settings by providing data for future targeted interventions to improve linkage to and retention in hepatitis C care among patients with TB.

Methods

Study design and setting

We analyzed the hepatitis C cascade of care among patients diagnosed with active TB disease and compared it to the cascade of care among people with HCV alone. TB-related information was obtained from the NTP of Georgia. Hepatitis C screening, diagnostic, and treatment information was obtained from the Georgian Hepatitis C Elimination Program.

Study population

The study population consisted of two groups: 1) Adults diagnosed with TB through the Georgian NTP from January 1, 2015, through December 31, 2019; and 2) Adults tested for

HCV antibodies in Georgia since January 1, 2015 who were not diagnosed with TB during 2015-2019. For both groups, hepatitis C testing and treatment information was obtained through September 30, 2020.

Hepatitis C cascade of care steps and definitions

We assessed the following steps in the hepatitis C cascade of care: 1) Screening for anti-HCV antibodies; 2) Viremia testing via ribonucleic acid (RNA) or core-antigen testing to confirm active HCV infection among those with HCV antibody positive result; 3) Hepatitis C treatment initiation among those with positive viremia test; 4) Hepatitis C treatment completion; 5) Eligibility for SVR – at least 12 weeks after treatment completion; 6) SVR result among those tested for SVR.

Two separate cascade of care analyses were performed among persons with HCV infection with and without TB disease. Hepatitis C cascade of care among patients with TB included the following groups: 1) Persons tested for anti-HCV antibodies at the time of or after their first TB diagnosis; and 2) Persons tested for anti-HCV antibodies before their TB diagnosis who did not initiate treatment for hepatitis C before their TB diagnosis. Hepatitis C cascade of care among patients without TB included the following groups: 1) Persons screened for HCV who were never diagnosed with TB during 2015-2019; and 2) Persons diagnosed with and treated for chronic HCV infection before they were first diagnosed with TB.

Patients were defined as LFU after a positive screening test if they had a positive HCV antibody test but did not undergo HCV viremia testing within the HCV elimination program and were still alive at the time of data extraction. Patients were defined as LFU

after an HCV viremia test if they had a positive result on viremia testing (i.e., positive RNA or core antigen test) and did not start treatment for HCV infection within the HCV elimination program. Due to lack of full drug-susceptibility testing data, patients with TB were defined as having MDR TB if they received TB treatment with second-line drugs which are used to treat MDR-TB.

Sources of data

All TB-related data were obtained from the Georgian NTP surveillance database. This database contains diagnostic and treatment-related information on every patient enrolled in the NTP. HCV screening information was obtained from the national HCV screening registry - a real-time, nationwide web-based system. The screening registry collects data from all stakeholders providing HCV screening throughout the country, including TB facilities. Data about HCV viremia testing, treatment, and treatment outcomes were obtained from the Hepatitis C Elimination Program clinical database, called "Elimination C" (ElimC).[164] ElimC collects information from all clinics providing hepatitis C diagnostic and/or treatment services to patients who undergo viremia testing after positive HCV antibody test result. If viremia testing is positive, further diagnostic test results and treatment-related information are entered in ElimC. Patients included in any of the three databases above were cross-checked in the National Death Registry and dates of death were obtained for patients found deceased. A unique patient identifier in all of these data sources is the national ID number, which was used as the linking variable.

Statistical analysis

In the main analysis evaluating the cascade of care, we calculated the proportions of people reaching each step of the hepatitis C care cascade, as described above. Next, we used survival analysis methods to explore if the time from a positive HCV screening test to viremia testing and time from a positive viremia test to hepatitis C treatment initiation was different between patients with and without TB. Patients were censored at the end of the follow-up period (September 30, 2020). Death was treated as a competing risk. Cumulative incidence curves were created to graphically examine the differences between the two groups, and Gray's test for equality of cumulative incidence functions was used to test for differences.[165,166]

An additional analysis was performed among patients with TB to identify demographic or TB-related factors associated with LFU in hepatitis C care after a positive antibody test or after a positive viremia test. Patients still on TB treatment were excluded from the analysis of LFU after positive confirmatory testing because they are ineligible for hepatitis C treatment until after TB treatment is completed. Patients with MDR TB were also excluded because eligibility for hepatitis C treatment in this group is heterogeneous – some patients start hepatitis C treatment while still on TB therapy, while others will have to wait until the TB treatment completion. We assessed if the following patient characteristics were associated with a higher risk of LFU from hepatitis C care: age, sex, region of residence, employment, TB case definition (new vs. previously treated case), and outcome of TB treatment (successful vs. unsuccessful). Log-binomial regression was used to calculate adjusted risk ratios and 95% confidence intervals for selected patient characteristics. Covariate selection was conducted a priori based on directed acyclic graph

(DAG) theory.[167] Different sets of covariates were used for each of the patient characteristics.

Results

Participants

A total of 14,993 records were obtained from the NTP database; 913 records (6.1%) were excluded due to a missing national ID number (Figure 1). Among patients whose observations were excluded, 73% were male and the median age was 38, compared to 70% males and the median age of 42 in the rest of the sample. The remaining 14,080 records corresponded to 12,767 individual patients, of which 11,985 (94%) were aged ≥18 and included in the analysis. Among those included (n=11,985), 70% were males, 82% were unemployed at the time of TB diagnosis, and 6.9% reported a history of incarceration. Among those with TB, 91% had one episode of TB treatment during the 2015-2019 period (i.e., diagnosed with TB only once), 7.9% had two episodes of TB treatment, and the remaining 1.6% had 3 to 8 episodes of TB treatment.

The hepatitis C screening registry contained data on 1,849,820 adults tested for HCV antibodies between January 1, 2015, and September 30, 2020, who were not diagnosed with TB in that period. The median age in this population was 46 years (IQR=31), and 54.8% were male.

Hepatitis C cascade of care among persons with and without TB

After obtaining the HCV testing information from the hepatitis C databases, 9,341 (78%)

of 11,985 persons with TB were found to have been tested for anti-HCV antibodies sometime between January 1, 2015 – September 30, 2020. Among these persons, 276 (3.0%) had already started treatment for HCV infection before their first TB diagnosis and were included in the care cascade analysis of patients without TB. The proportion of patients with TB tested for anti-HCV antibodies increased by year: among patients diagnosed with TB in 2015, 60% were tested for anti-HCV antibodies sometime during the study period. This proportion increased in each of the subsequent years and reached 90% among patients diagnosed with TB in 2019 (Table 1).

Among the total of 9,065 patients with TB who were tested for hepatitis C, 1,665 (18%) patients (Figure 1) had a positive antibody test, of which 7% died without undergoing viremia testing. Of the remaining 1,557 patients still alive, 1241 (80%) had viremia testing completed (Figure 2a). Of the 1,025 patients who had a positive viremia result, 443 (43%) were LFU prior to hepatitis C treatment initiation. For comparison, in the hepatitis C care cascade among patients without TB (Figure 2b), the proportion of patients who were LFU from hepatitis C care after positive antibody test or after positive viremia test were 14% and 19%, respectively. Patients with TB were also less likely to complete hepatitis C treatment (11% vs. 6%) and not get SVR testing (41% vs. 24%) compared to those who did not have TB. However, among those who completed hepatitis C treatment and were tested for SVR, the cure rate was comparable to those without TB (98.3% vs. 98.9%) (Figures 2a, 2b). Overall, among patients with confirmed active HCV infection, patients with TB were less likely to have a documented SVR achieved (28%) compared to patients without TB (55%; Figure 2c).

Timeliness of HCV viremia testing and treatment initiation

We compared the time from a positive screening test to viremia testing between 1,116 patients with TB and 97,554 patients without TB who had information on follow-up duration available. Overall, patients without TB who had information on follow-up duration available underwent viremia testing sooner than patients with TB (Hazards ratio [HR] = 1.46, 95% CI: 1.39, 1.54) (Figure 3). Among those who underwent viremia testing, the median time from antibody testing to viremia testing was 17 days (25^{th} and 75^{th} percentiles [Q1-Q3]: 3-248) among patients with TB and 6 (Q1-Q3: 1-24) among patients without TB.

We also compared time from positive viremia test to hepatitis C treatment initiation among 1,021 patients with TB and 87,964 patients without TB who had information on follow-up duration available (>99% of all persons with positive viremia test). Patients without TB started hepatitis C treatment sooner than patients with TB (HR=2.07, 95% CI: 1.91, 2.23) (Figure 4). Among those who started hepatitis C treatment, the median time from confirmation to treatment initiation was 176 days (Q1-Q3: 73-475) among patients with MDR TB, 132 days (Q1-Q3: 65-301) among patients with DS TB and 86 days (Q1-Q3: 56-203) among patients without TB.

Factors associated with LFU from hepatitis C care among patients with TB

Among patients with TB who had a positive HCV antibody test result, LFU before viremia testing was more common among females, patients enrolled in second-line TB treatment for drug-resistant TB and patients with unsuccessful or unknown TB treatment outcome. LFU at this step of hepatitis C care cascade substantially decreased among patients

diagnosed with TB in recent years, from 32% among patients diagnosed with TB in 2017 to 12% among patients diagnosed in 2019. In multivariable analysis, MDR TB was associated with increased risk of LFU after positive HCV antibody test (adjusted risk ratio [aRR]=1.41, 95% CI: 1.12, 1.76) (Table 2).

Among patients with DS TB who had confirmed active HCV infection, LFU before hepatitis C treatment initiation was more common among females, patients on first-line treatment and patients with successful TB treatment outcome. The proportion of patients LFU before hepatitis C treatment initiation increased by year, from 21% among patients diagnosed with TB in 2015 to 56% among patients diagnosed with TB in 2019. In the multivariable analysis, employment status, TB treatment outcome and new vs. previously treated TB were not associated with LFU before HCV treatment initiation (Table 3).

Discussion

In our study of two large-scale public health programs in the country of Georgia, we found that LFU from the hepatitis C care cascade was substantially more common among persons with TB compared to those without TB. Approximately 20% of persons diagnosed with TB in 2015-2019 who tested positive on anti-HCV antibodies did not have viremia testing for HCV infection, and more than 2 out of 5 patients with TB who had confirmed active HCV infection had not started hepatitis C treatment within the National hepatitis C Elimination program in Georgia. Our findings highlight the importance of improving linkage to hepatitis C diagnostic and treatment services among patients with TB.

LFU at different stages of hepatitis C care is a serious barrier in the control of HCV infection globally.[161] Georgia faces the same problem despite the existence of the

nationwide hepatitis C elimination program, which offers diagnostic and treatment services free of charge. Previous studies from Georgia have found that a high proportion of patients are LFU before viremia testing and before hepatitis C treatment initiation.[114,116] Our findings suggest that the issue of LFU from hepatitis C care is even more pronounced among patients with TB who are coinfected with HCV. Notably, among patients with TB, LFU before HCV viremia testing has decreased in recent years, which could be explained by a change in policy. According to the 2018 TB management guideline of Georgia, if an HCV antibody test is positive, blood samples are taken from the patient and sent for HCV viremia testing. Therefore, this policy change, coupled with full coverage of viremia testing by the government,[116] might have removed geographic, logistical, and financial barriers to viremia testing for patients with TB.

Furthermore, LFU before treatment initiation is also very common among patients with TB. Higher LFU before hepatitis C treatment initiation among patients with TB compared to those without TB could be explained by the fact that TB treatment is long (from 6 to 24 months), can be associated with severe adverse reactions, and, HCV treatment is usually not initiated until TB treatment is completed. Therefore, patients with TB might be more reluctant to start another long treatment course for hepatitis C due to treatment fatigue and previous negative experiences.[168] This issue has not been studied specifically among patients with both TB and HCV, but fatigue from diagnostic and treatment procedures as a risk factor for treatment discontinuation has been described among patients with TB and those with TB/HIV coinfection.[169-172] This is even more likely in the case of HCV infection without advanced liver damage because patients might not experience any symptoms associated with HCV infection; hence they might not feel the urgency to seek hepatitis C care.[87]

We also found that the proportion of patients LFU before hepatitis C treatment initiation is increasing by year, even if we look at the trend only among patients who completed treatment for TB. This could be explained by the fact that patients with TB diagnosed in recent years had less time to get enrolled in HCV elimination program after completing their TB treatment. Additionally, the COVID-19 pandemic and related restrictions in 2020 could have affected patients' ability and willingness to start treatment for hepatitis C.

Our findings suggest that patients with MDR TB were less likely to get HCV viremia testing compared to those with DS TB after a positive HCV antibody test. This finding may be explained by the fact that before the change in TB management guidelines in 2018, MDR patients were routinely tested for HCV infection in the TB facilities. In contrast, patients with DS TB were more likely to receive HCV screening either outside of TB facilities or if they had some indication for HCV testing when they were diagnosed with TB. Therefore, they would have more motivation to go through all steps in hepatitis C diagnosis.

Results from this study have potential implications globally for other countries that are trying to improve their hepatitis C and TB control programs. In 2015, Georgia became the first country in the world to initiate the nationwide hepatitis C elimination program, with significant progress achieved in scaling up HCV screening, diagnostic and treatment services in the whole country.[114] However, previously published literature and our analysis highlight that LFU from different stages of hepatitis C care poses a major challenge on the way to elimination goals, and patients with TB are even more likely to be LFU from hepatitis C care. To address the issue, stakeholders should consider introducing additional activities directed at more integrated care of HCV infection and TB, as well as

interventions targeted at the retention of patients in hepatitis C care, such as patient navigators. Additionally, patients with MDR TB could, in theory, be treated for HCV infection and TB concomitantly. There is no documented drug-drug interaction between DAAs used in HCV treatment and second-line TB drugs, and there are reports of successful implementation of co-treatment approach in small samples of patients.[148,173] Therefore, Georgia has a unique opportunity to achieve microelimination of HCV among patients with TB – a strategy that is proposed as a helpful approach for achieving the overall elimination goals.[174]

Our study has several limitations. First, due to the missing national ID number, we had to exclude 6% of observations from the NTP database and thus we are not aware of their hepatitis C testing and treatment status. Second, the limited number of variables in the hepatitis C screening registry and differences in variables available in hepatitis C and TB databases did not allow us to conduct more in-depth analysis to adjust for potential confounders for association of TB with LFU. For that reason, our time-to-event analysis is limited to crude comparison of cumulative incidence curves and crude hazards ratios between patients with and without TB.

In conclusion, we found that LFU from hepatitis C care after positive HCV antibody and viremia testing is more common among patients with TB compared to patients without TB. Existing large-scale public health programs for both TB and hepatitis C in Georgia create a unique opportunity for integrated care of these two infectious diseases that could potentially reduce the LFU, improve patient outcomes and contribute to achieving the national hepatitis C elimination goals.

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Table 2.1. HCV testing by year of first TB diagnosis, adult patients diagnosed with TB in 2015-2019.

	Patients diagnosed with TB	Ever Tested for HCV antibodies[a]		First HCV antibody testing before or during the last TB episode		First HCV antibody testing after last TB episode outcome		Ever tested positive for HCV antibodies	
Year	N	N	%	N	% (of total ever tested)	N	% (of total ever tested)	N	%
2015	2766	1671	60%	485	29%	1186	71%	414	25%
2016	2740	1860	68%	855	46%	1005	54%	410	22%
2017	2405	1948	81%	1610	83%	338	17%	333	17%
2018	2086	1791	86%	1635	91%	156	9%	255	14%
2019	1988	1795	90%	1773	99%	22	1%	253	14%

[a] excluding patients who started treatment for HCV infection before first TB diagnosis

Abbreviation: HCV, hepatitis C virus; TB, tuberculosis

Table 2.2 Risk factors for loss to follow-up from HCV care before HCV viremia testing among patients with TB.

Study population: patients diagnosed with TB in 2015-2019 who had a positive HCV antibody test result. Comparison groups: 1) Patients with TB underwent HCV viremia testing (not LFU) and, 2) Patients with TB who did not undergo viremia testing and are still alive (LFU). HCV viremia testing status ascertained as of September 30, 2020. Patients with positive HCV antibody test who died are excluded from this analysis.

CHARACTERISTICS (based on first TB diagnosis)	**Total (N=1557)**		**LFU (n=318)**		**Not LFU (n=1239)**		**cRR (95%CI)**	**aRR (95%CI)**
	N	**%**	**N**	**%**	**N**	**%**		
Sex								
Male	1411	91%	273	19%	1138	81%	1	
Female	146	9%	45	31%	101	69%	1.59 (1.22, 2.08)	
Age								
Median (IQR)	45 (16)		43 (16)		46 (16)			
Region								
Tbilisi	620	40%	138	22%	482	78%	1	
Other	885	57%	173	20%	712	80%	0.88 (0.72, 1.07)	
Penitentiary system	52	3%	7	13%	45	87%	0.60 (0.30, 1.22)	
Employment status								
Employed	155	10%	34	22%	121	78%	1	1

Unemployed	1344	86%	276	21%	1068	79%	0.94 (0.68, 1.28)	0.95 (0.69, 1.30)[a]
Military	2	0%	0	0%	2	100%	-	
Missing	56	4%	8	14%	48	86%	-	
IDP								
Yes	131	8%	37	28%	94	72%	1.44 (1.07, 1.93)	
No	1342	86%	263	20%	1079	80%	1	
Missing	84	5%	18	21%	66	79%	-	
History of imprisonment								
Yes	295	19%	55	19%	240	81%	0.91 (0.70, 1.18)	
No	1192	77%	245	21%	947	79%	1	
Missing	70	4%	18	26%	52	74%	-	
TB DIAGNOSIS AND TREATMENT								
Year of TB diagnosis								
2015	386	25%	64	17%	322	83%	1.35 (0.90, 2.02)	
2016	374	24%	76	20%	298	80%	1.65 (1.12, 2.44)	
2017	304	20%	97	32%	207	68%	2.60 (1.79, 3.77)	
2018	249	16%	51	20%	198	80%	1.67 (1.10, 2.52)	
2019	244	16%	30	12%	214	88%	1	
# of TB Tx episodes								

1	1303	84%	272	21%	1031	79%	1	
2+	254	16%	46	18%	208	82%	0.87 (0.65, 1.15)	
Newly diagnosed TB								
Yes	1066	68%	217	20%	849	80%	1	1
No/Unknown	491	32%	101	21%	390	79%	1.01 (0.82, 1.25)	1.07 (0.86, 1.34)[b]
MDR TB								
Yes	277	18%	75	27%	202	73%	1.43 (1.14, 1.78)	1.41 (1.12, 1.76)[c]
No	1280	82%	243	19%	1037	81%	1	1
Treatment outcome								
Successful	985	63%	184	19%	801	81%	1	1
Unsuccessful/Unknown	509	33%	125	25%	384	75%	1.31 (1.08, 1.61)	1.10 (0.84, 1.45)[d]
Missing	63	4%	9	14%	54	86%	-	

Abbreviations: TB, tuberculosis; HCV, hepatitis C virus; LFU, loss to follow-up; cRR, crude risk ratio; aRR, adjusted risk ratio; IQR, interquartile range; IDP, internally displaced person; Tx, treatment; MDR, multidrug-resistant TB.

[a] adjusted for age, sex, IDP, MDR TB, case definition (new vs. previously treated);

[b] adjusted for age, sex, MDR TB, employment status;

[c] adjusted for age, sex, case definition (new vs. previously treated);

[d] adjusted for age, sex, MDR TB, employment status;

Table 2.3 Loss to follow-up from hepatitis C care before treatment initiation among patients with drug-susceptible TB. Study population: patients diagnosed with drug-susceptible TB in 2015-2019 who have confirmed HCV infection. Comparison groups: 1) Patients with TB who started HCV treatment, and 2) Patients with TB who are eligible but did not start HCV treatment as of September 2020. Patients with positive HCV viremia test who died or are still on TB treatment are excluded from this analysis.

CHARACTERISTICS (based on first TB diagnosis)	**Total (N=758)**		**LFU before hepatitis C treatment (n=259)**		**Hepatitis C treatment started (n=499)**		**cRR (95%CI)**	**aRR (95%CI)**
	N	**%**	**N**	**%**	**N**	**%**		
DEMOGRAPHIC CHARACTERISTICS								
Sex								
Male	694	92%	230	33%	464	67%	1	
Female	64	8%	29	45%	35	55%	1.37 (1.02, 1.83)	
Age								
Median (IQR)	45 (15)		46 (16)		44 (14)			
Region								

Tbilisi	290	38%	95	33%	195	67%	1	
Other	441	58%	157	36%	284	64%	1.09 (0.88, 1.34)	
Penitentiary system	27	4%	7	26%	20	74%	0.79 (0.41, 1.53)	
Employment status								
Employed	75	10%	25	33%	50	67%	1	
Unemployed	647	85%	218	34%	429	66%	1.01 (0.72, 1.42)	0.93 (0.67, 1.30)[a]
Military	2	0%	1	50%	1	50%	-	
Missing	34	4%	15	44%	19	56%	-	
IDP								
Yes	67	9%	22	33%	45	67%	0.97 (0.68, 1.39)	
No	655	86%	221	34%	434	66%	1	
Missing	36	5%	16	44%	20	56%		
History of imprisonment								
Yes	597	79%	47	36%	84	64%	1.05 (0.81, 1.35)	
No	131	17%	204	34%	393	66%	1	
Missing	30	4%	8	27%	22	73%		
TB DIAGNOSIS AND TREATMENT								
Year of TB diagnosis								

2015	193	25%	41	21%	152	79%	1	
2016	199	26%	46	23%	153	77%	1.09 (0.75, 1.58)	
2017	135	18%	47	35%	88	65%	1.64 (1.15, 2.34)	
2018	117	15%	61	52%	56	48%	2.45 (1.78, 3.39)	
2019	114	15%	64	56%	50	44%	2.64 (1.93, 3.63)	
# of TB Tx episodes (binary)								
1	647	85%	231	36%	416	64%	1	
2+	111	15%	28	25%	83	75%	0.71 (0.50, 0.99)	
Newly diagnosed TB								
Yes	555	73%	193	35%	362	65%	1	1
No/Unknown	203	27%	66	33%	137	67%	0.93 (0.74, 1.18)	0.92 (0.72, 1.16)[b]
Treatment outcome (binary)								
Successful	611	81%	214	35%	397	65%	1.09 (0.84, 1.42)	1.04 (0.79, 1.38)[c]
Unsuccessful/Unknown	137	18%	44	32%	93	68%	1	1
Missing	10	1%	1	10%	9	90%	-	

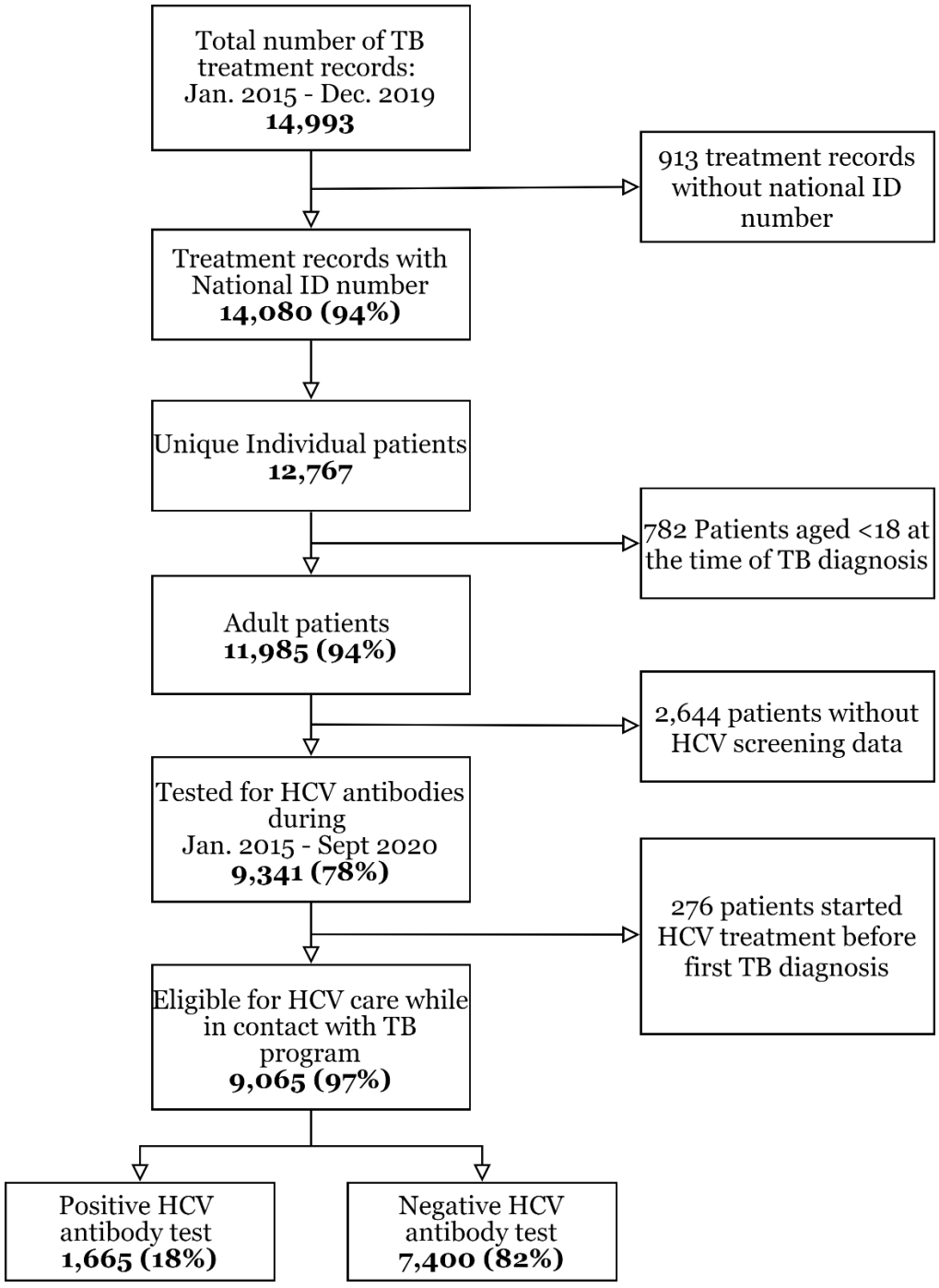
Abbreviations: TB, tuberculosis; HCV, hepatitis C virus; LFU, loss to follow-up; cRR, crude risk ratio; aRR, adjusted risk ratio; IQR, interquartile range; IDP, internally displaced person; Tx, treatment;

a adjusted for age, sex, IDP, case definition (new vs. previously treated);

b adjusted for age, sex, employment status;

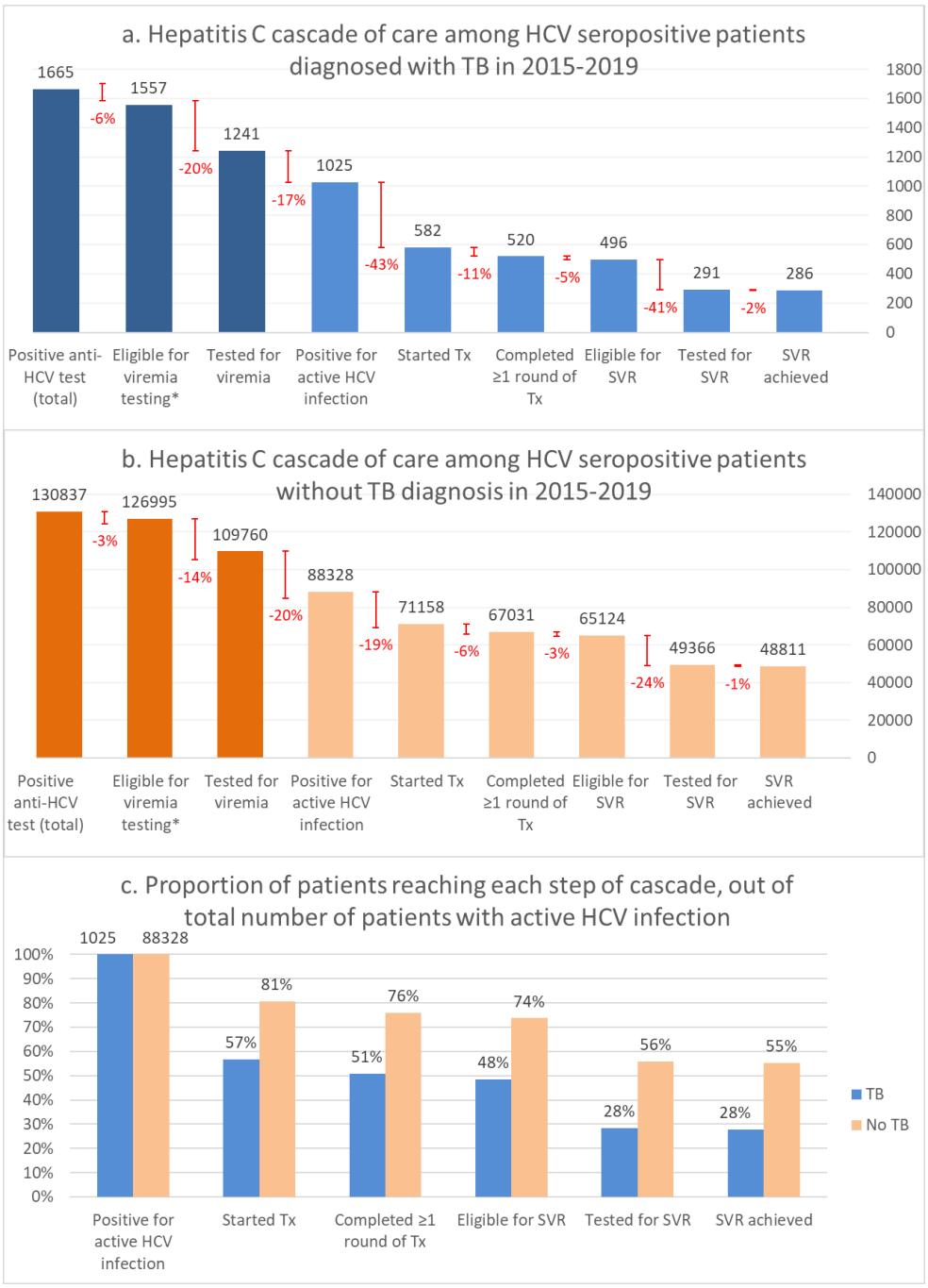
c adjusted for age, sex, employment status;

Figure 2.1. Flow chart of patients with TB and their HCV screening status - 2015-2019



Abbreviation: HCV, hepatitis C virus; TB, tuberculosis;

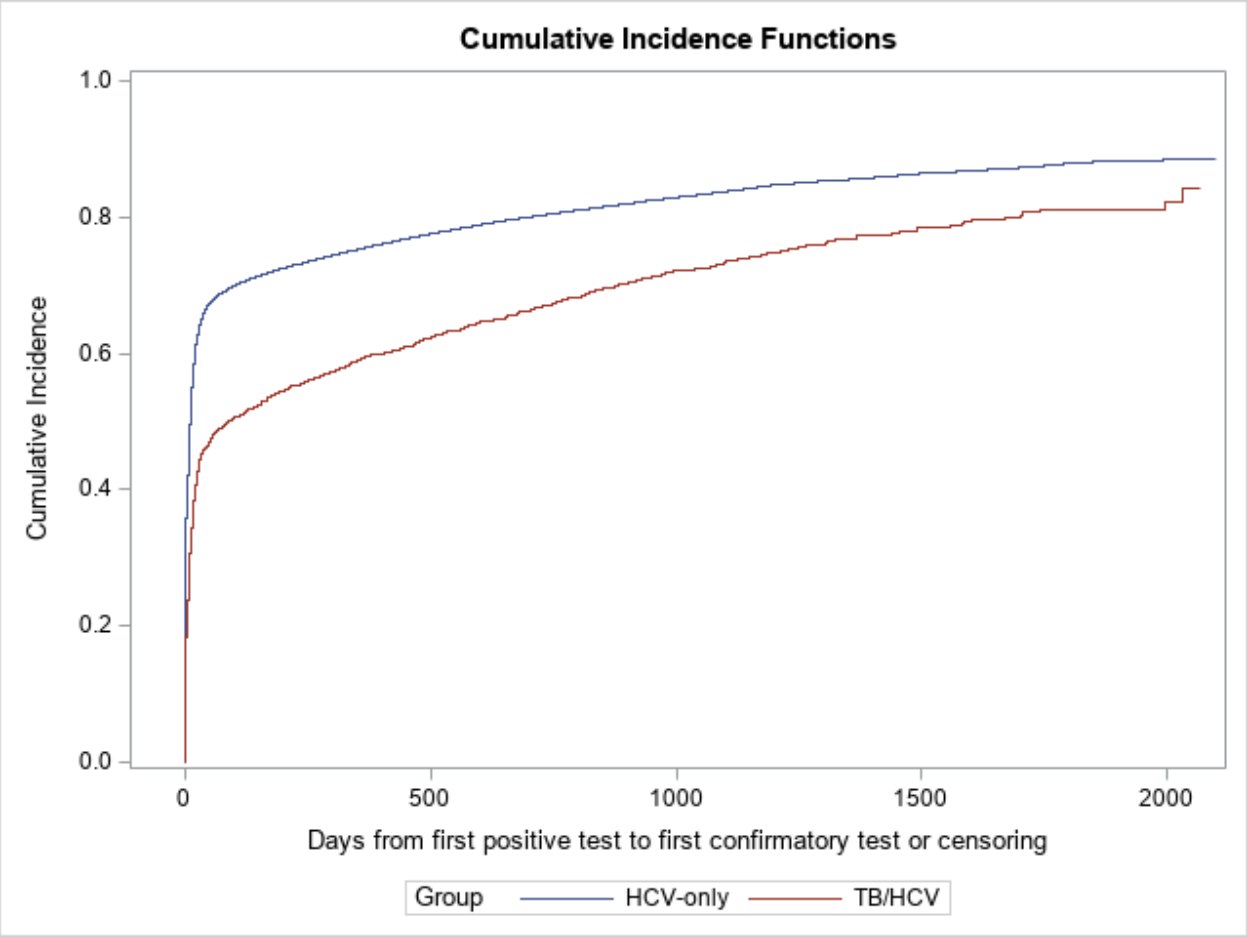
Figure 2.2. Hepatitis C cascade of care among patients with and without tuberculosis.



* No death before viremia testing

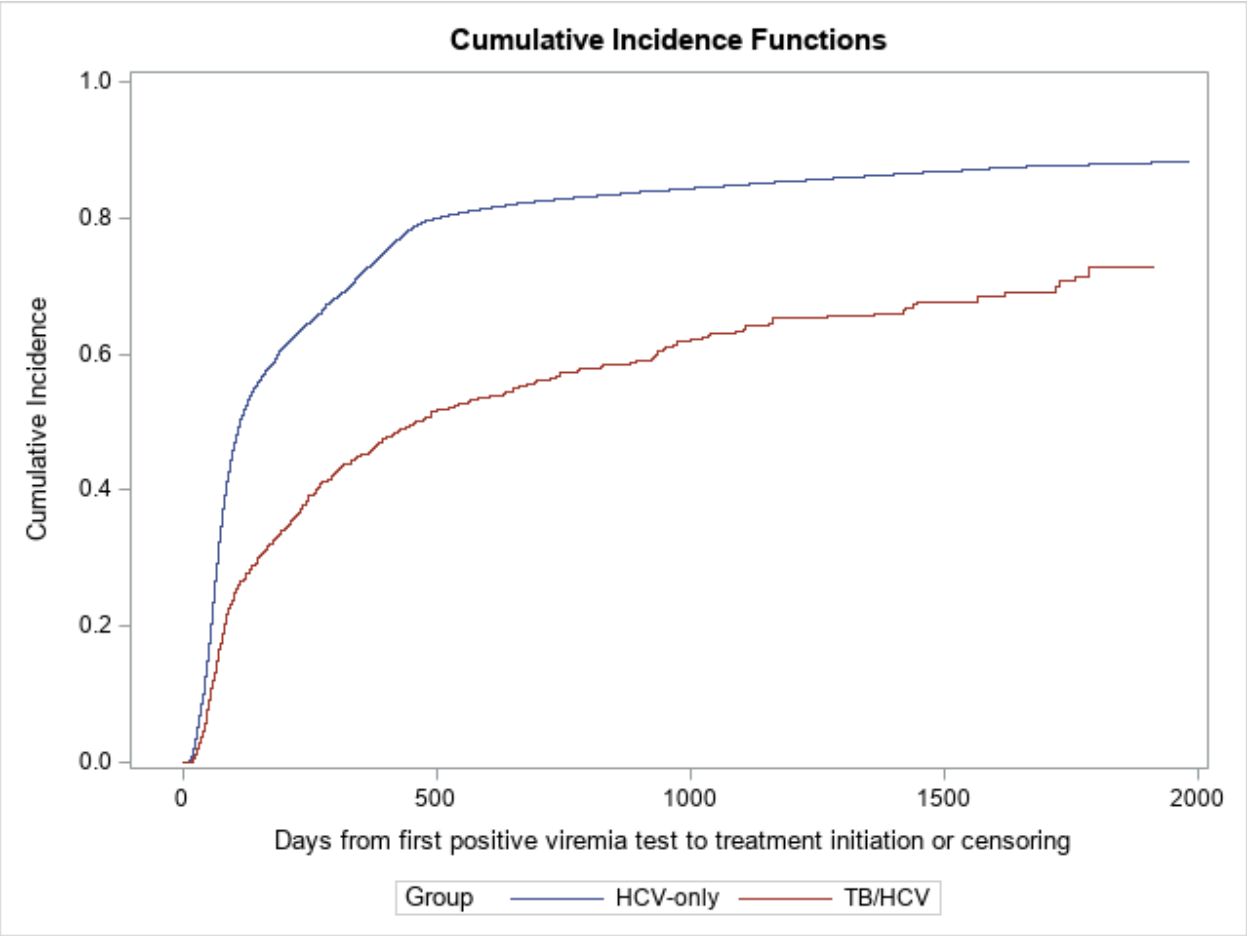
Abbreviation: HCV, hepatitis C virus; TB, tuberculosis; SVR, sustained virologic response.

Figure 2.3. Comparison of HCV viremia testing cumulative incidence among HCV seropositive patients with and without TB - January 1, 2015 – September 30, 2020.



Notes: Blue line corresponds to the patients with confirmed HCV infection without evidence of TB diagnosis in 2015-2019. Red line corresponds to patients with confirmed HCV infection diagnosed with TB in 2015-2019. Gray's test p-value<0.001.

Figure 2.4. Comparison of cumulative incidence of HCV treatment initiation among patients with confirmed HCV infection with and without TB - January 1, 2015 – September 30, 2020.



Notes: Blue line corresponds to patients with confirmed HCV infection without evidence of TB diagnosis in 2015-2019. Red line corresponds to patients with confirmed HCV infection diagnosed with TB in 2015-2019. Gray's test p-value<0.001

Chapter 3: Association of treated and untreated HCV infection with active tuberculosis disease

Abstract

Background: Hepatitis C virus (HCV) infection causes dysregulation and suppression of immune pathways involved in the response against and control of tuberculosis (TB) infection. However, data on the role of chronic hepatitis C as a risk factor for active TB disease is lacking. The country of Georgia's novel program for hepatitis C elimination and national databases for both HCV and TB provide a unique opportunity to explore the incidence of TB disease among HCV-infected persons. We sought to evaluate the association of HCV infection on the rate of TB disease.

Methods: We conducted a cohort study among adult residents of the country of Georgia tested for HCV antibodies between January 1, 2015 and September 30, 2020. Data were obtained from the Georgian hepatitis C elimination program, National TB Program, and national death registry electronic databases and linked using a unique national ID. The exposure of interest was the status of HCV infection, with three categories: (1) HCV antibody-negative (reference group); (2) completed HCV treatment (treated); (3) untreated HCV infection. The outcome was newly diagnosed TB disease. Follow-up started at HCV antibody testing and ended at time of first TB diagnosis, death, or end of the study period. Crude incidence rates and 95% confidence intervals (CI) were calculated. To calculate adjusted hazards ratios (aHR) and 95% CIs, we used a stratified Cox model with HCV status treated as a time-varying covariate, adjusted for sex, incarceration, and municipality of residence, stratified by birth cohort.

Results: A total of 1,828,808 adults were included, with a median follow-up time of 26 months (Q1-Q3: 13-39 months). TB was diagnosed in 3,163 (0.17%) participants after a median of 6 months (Q1-Q3: 1-18 months). The TB incidence rate was 65 cases per 100,000 person-years (PY) among HCV-negative persons, 109 cases per 100,000 PY among those treated for HCV infection, and 296 cases per 100,000 PY among persons with untreated HCV infection. In multivariable analysis, both untreated (aHR=2.9, 95%CI: 2.4, 3.4) and treated (aHR=1.6, 95%CI: 1.4, 2.0) HCV infection were associated with a higher hazard of active TB, compared to HCV-negative persons.

Conclusion: Adults with HCV infection were at higher risk of developing active TB disease. Our findings suggest that screening for latent TB infection and TB disease should be considered in the process of clinical evaluation of people with HCV infection, especially in high TB burden areas; this could contribute to the prevention of TB disease, which is one of the priorities of World Health Organization's End TB strategies.

Introduction

Tuberculosis (TB) emerged as the leading cause of death due to a single infectious agent before the COVID-19 pandemic, exceeding that due to HIV infection. In 2019, an estimated 10 million people developed active TB disease, and there were 1.4 million deaths due to TB.[1] Additionally, an estimated 1.7 billion people worldwide are infected with *Mycobacterium tuberculosis (Mtb)*, the causative agent of TB, and are potentially at risk of developing active TB sometime in their lifetime.[9] Hepatitis C virus (HCV) infection is also a major public health problem globally. According to 2019 WHO estimates, there are 58 million people living with chronic hepatitis C, 1.5 million new cases occur each year, and 290,000 people died due to hepatitis C in 2019.[158] The hepatitis C epidemic affects all parts of the world, with the highest prevalence in the Eastern Mediterranean and European regions.[63] Despite the substantial overlap in population subgroups affected with HCV and TB, the impact of chronic HCV infection on the risk of active TB is not well established.

Risk factors for progression from latent TB infection (LTBI) to active TB include immunocompromising conditions such as HIV infection, diabetes, smoking, and organ transplantation.[10] HCV infection also causes dysregulation and suppression of immune pathways involved in the response and control of *Mtb*, including an impairment of cytokines responsible for macrophage activation and T-cells involved in direct destruction of *Mtb*.[134,135,137-139] However, the role of HCV infection as a risk factor for active TB has not been extensively studied in real-life settings. Some studies suggest that those with chronic HCV infection are also at higher risk of tuberculosis,[22] but compelling evidence is lacking due to limited data. Due to this knowledge gap, testing for latent and active TB or

preventive measures are usually not undertaken among patients diagnosed with chronic hepatitis C.

The Eastern European country of Georgia (population 3.7 million) provides a unique opportunity to explore how HCV infection affects the development of active TB, with large-scale public health programs in place for both diseases. Georgia is designated as a high-priority country for TB control in the WHO European Region,[16,55] with an estimated incidence of 74 cases per 100,000 population in 2019.[1] All diagnostic and treatment procedures (including medications) for both drug-susceptible and drug-resistant TB are provided free of charge within the Georgian National TB Program. TB surveillance data is collected in a centralized National TB Program database at the National Center for Tuberculosis and Lung Diseases (NCTLD).[175]

Chronic HCV infection is also highly prevalent in Georgia, affecting 5.4% of the general adult population (~150,000 individuals) based on 2015 prevalence estimates – the highest prevalence among Eastern Europe and Central Asia countries and among the ten countries with the highest prevalence worldwide.[90,111,112] In 2015, with support from the US Centers for Disease Control and Prevention (CDC) and other international partners, Georgia became the first country to formally implement a nationwide program to eliminate hepatitis C. The program provides free hepatitis C testing and treatment with an all oral regimen of directly acting antivirals (DAAs) for all citizens.[113-115] The country integrated hepatitis C screening through HCV antibody (anti-HCV) testing into multiple existing programs and settings, such as blood safety, antenatal surveillance, harm reduction, inpatient settings, prisons, and national HIV and TB programs.[114,116-119] Similar to TB, hepatitis C screening and clinical information is entered into nationwide

databases.[116]

The objective of this study was to assess how chronic HCV infection status affects the rate of active TB disease. The prespecified hypothesis was that the incidence of active TB was highest among those with chronic HCV infection who have not been treated; we hypothesized that the incidence would be lower in those who had chronic HCV infection but received treatment, and the lowest among HCV-uninfected persons. The large scale of the Georgian hepatitis C elimination program and nationwide screening activities allowed us to compare TB incidence rates between all three groups of interest. Finding an association between HCV infection and increased risk of TB would provide a rationale to introduce routine screening for LTBI and active TB among persons with HCV infection in line with the WHO-initiated End TB Strategy, which calls for integrated, patient-centered care and systematic screening of contacts and high-risk groups.[17]

Methods

Study design and population

We conducted a cohort study among all adult residents of Georgia tested for anti-HCV antibodies. The study period was January 1, 2015 – September 30, 2020. Exclusion criteria were (1) missing national ID number in the anti-HCV testing data, (2) missing or incorrect dates necessary for incidence calculations (dates of anti-HCV testing, death, or hepatitis C treatment completion), and (3) diagnosis of TB before or at the time of the first anti-HCV antibody testing. Several groups were included in initial descriptive analysis and incidence calculations but excluded from multivariable models due to the inability to classify them into one of the three main categories of interest. These included

study participants with (1) conversion of anti-HCV test results (i.e., from HCV negative to HCV positive) during the study period; (2) a positive anti-HCV test result, but a negative HCV viremia test (PCR or core antigen) and no evidence of previous treatment in the elimination program; (3) a positive anti-HCV test result without a viremia test. More details about the selection of the study population are provided in Appendix A.

Data sources

Hepatitis C testing and treatment information was obtained from two nationwide electronic databases: the national HCV screening registry; and hepatitis C elimination program clinical database "Elimination C" (ElimC). The outcome variable (diagnosis of TB) was ascertained from the national TB surveillance database managed by the NCTLD. Mortality data was extracted from the national death registry and date of death was obtained for deceased individuals, but cause of death was not available. The linking variable was the national ID number – a unique identifier used in all databases above.

Variables and definitions

The baseline date was defined as the date of the first known anti-HCV testing. If a person tested during the study period also had a testing record from before 2015 with the same result, the baseline date was set at January 1, 2015. Persons with HCV viremia were defined as treated for hepatitis C if they finished the hepatitis C treatment course within the hepatitis C elimination program, and as untreated otherwise. If a person had more than one episode of hepatitis C treatment (i.e., reinfection or re-treatment after treatment failure), the treatment completion determination was based on the latest hepatitis C

treatment. Persons were defined as having an active TB if they had clinically or laboratory confirmed TB diagnosed within the National TB Program between the baseline date and September 30, 2020, without history of previous TB diagnosis.

Statistical analysis

Incidence rates of active TB disease were calculated in different socio-demographic groups, as well as in five groups with different HCV infection status: (1) Persons with no evidence of HCV infection (negative result on anti-HCV test); (2) Persons with HCV infection, but successfully completed HCV treatment; (3) Persons with untreated HCV infection; (4) Persons with anti-HCV antibodies without viremia testing; (5) Persons with anti-HCV antibodies and negative viremia result. Person-time was calculated by counting the number of days from the baseline date to the first occurrence of either (1) first TB diagnosis, (2) death, or (3) end of the study period (September 30, 2020). Persons treated for HCV infection contributed person-time to both treated and untreated groups, with the date of the last HCV treatment completion used as a switching point. Crude incidence rate ratios and 95% confidence intervals were calculated in five groups of different HCV status, with persons with no evidence of HCV infection serving as a reference group.

In multivariable analysis, a Cox proportional hazards regression model was used to calculate adjusted hazards ratios (aHR) and 95% confidence intervals. The model used age as a time-scale and was stratified on birth cohort (5-year intervals) to adjust for the birth cohort effects. The primary exposure of interest was the status of HCV infection with three categories: (1) absence of HCV infection (reference category); (2) Treated HCV infection; (3) Untreated HCV infection. The primary outcome of interest was newly

diagnosed active TB disease during the follow-up period. Follow-up time started at the baseline date. Participants were censored at death or at the end of follow-up (September 30, 2020). Hepatitis C treatment was treated as a time-varying variable: treated individuals contributed follow-up time to the untreated group until completing the hepatitis C treatment, at which point they moved to the treated group. Additional variables were selected for inclusion in the model based on directed acyclic graph theory (figure 2).[167]

A substantial proportion of persons who had a positive result on the anti-HCV test did not undergo the viremia testing. If this portion of patients is different from people who underwent confirmatory testing in terms of their hepatitis C status and the risk of TB, there is potential selection bias. To address this issue, we conducted inverse probability of selection weighting. Study participants with confirmatory testing were reweighted so that they represent themselves, plus some of the persons in the source population who were eligible but not included in the final analysis (i.e., tested for anti-HCV, but not for viremia).[176] The weights were derived based on age, sex, municipality, and imprisonment status. Multivariable analysis with extended cox models was conducted using these weights.

Sensitivity analysis

We conducted a sensitivity analysis to explore how the findings might have changed using several different assumptions and definitions. For this purpose, we ran three additional multivariable models with varying assumptions. In the first sensitivity analysis model, we repeated the multivariable model using the date of the first hepatitis

C treatment initiation as a switching point between treated and untreated states for patients who received hepatitis C treatment. In the second model, we excluded patients treated for hepatitis C infection who did not achieve sustained virologic response (SVR) – an indicator for cure. In the third model, we excluded patients treated for hepatitis C who either did not achieve SVR or did not get tested for SVR, i.e., the treated group only included patients with documented SVR.

Quantitative bias analysis

We conducted quantitative bias analysis for unmeasured confounding due to injection drug use (IDU), a well-known risk factor for HCV infection and active TB. IDU status was not universally available in our data sources for the whole study population. We conducted bias analysis and adjustment using the methods previously described.[177] The following bias analysis parameters were specified based on the review of published literature: effect of injection drug use on rate of active TB on a hazards ratio scale (U), conditional on exposures and other covariates, and prevalence of injection drug use among three comparison groups (P_1, P_2, and P_3). The bias factor on the hazard ratio scale was calculated by the formula: $\frac{1+(U-1)*P_i}{1+(U-1)*P_1}$, where i=2, 3 for untreated and treated categories. The bias-adjusted hazards ratio was then derived by dividing the observed aHR by the bias factor. We also conducted the sensitivity analysis of bias analysis in which we varied the parameter estimates for U and P. Full details about parameter estimates used for quantitative bias analysis are provided in appendix B.

Results

Description of the study population

The initial study population consisted of 1,849,678 adults tested for anti-HCV antibodies during the study period. We excluded 12,156 (0.7%) persons with previous or current TB at the time of anti-HCV antibody testing, and 8,714 (0.5%) persons with missing or incorrect date variables necessary for calculating person-times. The remaining 1,828,808 people were included in the initial descriptive analyses and incidence calculations (**Figure 1**). Forty-five percent were male, and the median age was 46 (25^{th} and 75^{th} percentiles [Q1-Q3]: 31-62). Most people were tested for anti-HCV antibodies in an outpatient setting (54%), inpatient setting (13%), or at a blood bank (10%) (**Table 1**). The median follow-up time was 26 months (Q1-Q3: 13-39), with a total of 4,212,327 person-years of follow-up. People who had a conversion of anti-HCV antibody testing results (n=17,323) or those with positive anti-HCV testing results with negative or missing viremia testing (n=33,128) were retained in descriptive analysis but excluded from the primary multivariable models (**Figure 1**).

Active TB by HCV status

There were 3,163 (0.17%) individuals newly diagnosed with active TB among our analytic cohort of 1,828,808 individuals; this equated to a TB incidence rate of 75.1 per 100,000 person-years (**Table 1**). The incidence of newly diagnosed active TB was more than four times higher among people with untreated HCV infection (296 cases per 100,000 PY, 95% CI: 264, 331), and 1.7-times higher among people treated for HCV (109.1 cases per 100,000 PY, 95%CI: 93.1, 127.1) compared to those never infected with HCV infection (65

cases per 100,000 PY, 95% CI: 62, 68). Compared to those never infected with HCV, the incidence of TB was two times higher among people with a positive anti-HCV result result and negative viremia test (141 cases per 100,000 PY, IRR 2.1) and three times higher among people with positive anti-HCV test result who did not undergo viremia testing (216 per 100,000 PY, IRR 3.3; **Table 2**).

In the multivariable analysis including the three main groups of people with known HCV status (uninfected, treated, and untreated HCV infection), those with untreated HCV infection were at greatest risk for active TB disease (aHR=2.9, 95% CI 2.4, 3.4) as compared to persons never infected with HCV (**Table 3**). Individuals with HCV who were treated also had an increased risk of active TB (aHR=1.7, 95% CI 1.4, 2.0) although it was less than those with untreated HCV.

The precise adjusted hazard ratios (aHR) of our findings changed only slightly in the three sensitivity analysis models (**Table 3**). The aHR comparing untreated and uninfected groups remained 2.9-3.0 in all sensitivity analyses. Even though the definition of the HCV treated group changed in each sensitivity analysis, treated HCV consistently had a substantially lower hazard of active TB diagnosis than those with untreated HCV – with the greatest reduction in hazard seen in the most conservative definition of the treated group, where we included only patients with documented SVR (i.e., Sensitivity analysis 3: aHR 1.5, 95% CI 1.2, 1.9; **Table 3**).

Quantitative bias analysis and bias adjustment

In quantitative bias analysis and adjustment for unmeasured confounding IDU, we observed the shift of the estimated measures of association towards the null for both treated and untreated groups. The aHR for the untreated group remained close to 2.0

even for the most conservative estimates of bias parameters. However, it reaches the null association for the treated group for the sensitivity analysis scenarios when we increase the estimate for the prevalence of IDU among treated HCV (Table 4).

Discussion

In this study, we sought to assess the impact of chronic HCV infection on the risk of developing active TB disease. We used national HCV and TB databases in the country of Georgia, where an unprecedented nationwide HCV elimination program is taking place which allowed us a unique opportunity to evaluate the impact of HCV on active TB risk in a nationwide cohort of 1,828,834 people. To our knowledge, this is the most extensive cohort study to date that have evaluated the relationship between HCV and the risk of developing TB disease and the first to compare TB occurrence specifically among people treated with new DAAs. We found that the incidence of active TB was higher in all groups with hepatitis C, with the highest incidence among people with untreated hepatitis C. We observed a strong association, in multivariable analysis, where untreated hepatitis C resulted in almost three times higher risk of developing active TB; this association held in all sensitivity analyses and after bias-adjusting for IDU as an unmeasured confounder. Treated hepatitis C was also associated with active TB, although the effect was smaller and attenuated after sensitivity analyses and bias adjustment for IDU. This findings suggest that the increased risk of TB is caused by the active HCV infection itself and not by its sequelae or other unmeasured factors.

Our findings suggest that chronic HCV infection may be causally associated with the development of active TB. Definitive claims about the causal nature of this association cannot be made due to unmeasured and unknown confounders, such as social and

behavioral factors that increase the risk of HCV infection and active TB. However, such causal association is biologically plausible. Through its effects on a host's immune system, HCV can increase an individual's risk of TB in two ways: (1) by increasing susceptibility to TB disease upon initial exposure to Mtb, and (2) by increasing the risk of progression from LTBI to active TB disease. In a recent study, patients with both TB and hepatitis C had lower expression of markers of CD4 T-cell activation compared to patients with only TB or hepatitis C.[133,134] Additionally, there are several hypothetical immunological mechanisms by which HCV might affect the risk of TB: (1) chronic HCV infection reduces the production and concentration of several cytokines (e.g. interferon-gamma [IFN-γ] and tumor necrosis factor alpha [TNF-α]) involved in the activation of macrophages, which are essential for effective control of *Mtb* infection;[5,137,29] (2) HCV infection increases the level of inhibitory cytokines, such as interleukin-10 (IL-10), which inhibits cytokines required for an effective response to Mtb including IL-12, IFN-γ, and TNF-α;[138] (3) HCV infection also affects Natural Killer (NK) cells by reducing their direct cytotoxic activity against bacteria and their capability of producing cytokines involved in immune pathways against *Mtb* infection. NK cells are increasingly recognized as important actors in the immune response against *Mtb*;[139,141,142] (4) viral persistence during chronic hepatitis C can cause the development of functionally inferior T cells – a condition referred to as T-cell exhaustion.[143-147] This condition affects the ability of CD8 T cells to produce and release adequate amounts of inflammatory mediators, including IFN-γ and perforin, thus impairing the direct destruction of *Mtb*.[135]

Our findings do not allow us to make any conclusive claims about the association between treated hepatitis C and active TB. Overall, in crude incidence comparisons and multivariable models, we found that the rate of active TB among those treated for

hepatitis C was higher than that among persons without HCV infection. However, this association was weaker for treated hepatitis C compared to untreated hepatitis C, and tended to shift towards null association in sensitivity analyses and bias analysis. Immunologic studies in patients after DAA treatment show conflicting results. Some studies suggest there is a partial improvement of immune functions after SVR, while others did not demonstrate any reconstitution in CD8 T cell functions and IFN-γ production.[178,179] Our findings support the hypothesis that there is improvement in immune functions responsible for *Mtb* control among patients treated for HCV with DAAs, suggesting the indirect benefit of DAA treatment on the risk of developing active TB disease.

Our results are consistent with the finding of a cohort study from Taiwan that reported an association between hepatitis C and active TB (aHR 3.2, 95% CI: 1.85, 5.53). However, the study from Taiwan did not distinguish between treated and untreated hepatitis C. Another study from Taiwan compared TB rates in patients with HCV infection with or without interferon-based regimens (primary treatment regimen before DAAs became available). The overall incidence of TB in patients with HCV was approximately twice higher than overall TB incidence in Taiwan. They did not find any statistically significant difference in TB incidence between treated and untreated patients, although this could be due to low number of people found with TB during the follow-up period (3 and 5 patients in treated and untreated groups, respectively).[180]

Our study suggests that people with hepatitis C should be included as one of the priority groups for TB control efforts. This has at least two important implications for TB programs: (1) Integration of active TB screening measures for patients diagnosed with

hepatitis C could potentially increase TB case detection. Diagnostic and treatment delay is an impediment to TB control both globally and in Georgia.[61,181] Identifying an additional risk group that could benefit from the routine screening will help in timely diagnosis and prevention of active TB and would thus contribute to decreasing the overall TB incidence in Georgia; (2) Patients with hepatitis C could be prioritized for preventive measures, such as educational interventions about TB, or treatment for LTBI among those who do not have contraindications. This is in line with the new WHO guideline recommending scaling up treatment of LTBI and expanding the groups who should be treated.[15] However, LTBI testing or treatment is currently not prioritized for patients with chronic hepatitis C in Georgia.

Our study had several limitations: (1) Our data did not include some variables that can confound the associations between HCV and TB, such as IDU and socioeconomic status. We tried to alleviate this issue by adjusting for municipality as a proxy variable for socioeconomic status, and by using quantitative bias-analysis methods to adjust for IDU as a confounder; (2) Our data only captured reported diagnosed active TB cases, therefore, people with undiagnosed TB might have been misclassified as free of TB. Therefore, the incidences of active TB in our results might be underestimated; (3) We did not have data on the emigration status of our study participants, which might have caused misclassification of both, exposure and outcome. Some people that were classified as "untreated" for hepatitis C in our study, might have received treatment outside the country. However, Georgian HCV Elimination Program offers free treatment with the highly effective oral regimens for every citizen of the country, therefore, this scenario is highly unlikely. Additionally, if people who emigrated from Georgia died or were diagnosed with active TB, they would be kept in our study population till the end of the

study period, thus inflating the risk set and decreasing the TB incidence estimates.

In conclusion, in this large population-based cohort study involving 1.8 million adults, we found a strong association between untreated hepatitis C and development of active TB. Our findings suggest that screening for latent TB infection and TB disease, as well as preventive TB treatment among those with LTBI should be considered in the clinical evaluation of people with HCV infection. This could reduce TB incidence and improve early detection of TB disease, which are priorities of the World Health Organization's End TB strategies.

Funding

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Table 3.1 Descriptive statistics of study population and incidence of newly diagnosed active TB: adults tested for anti-HCV antibodies in Georgia in 2015-2019 without prior TB diagnosis

DEMOGRAPHIC CHARACTERISTICS	Total		New active TB			TB IR per
	N	% (column)	N	% (row)	PY	100,000 PY
Total Cohort	**1,828,808**	**100%**	**3,163**	**0.17%**	**4,212,327**	**75.1**
Sex						
Male	825,081	45%	2085	0.25%	1,962,556	106.2
Female	1,003,727	55%	1078	0.11%	2,249,771	47.9
Year of first anti-HCV testing						
<2015	68,140	4%	243	0.36%	388,635	62.5
2015	68,540	4%	224	0.33%	348,813	64.2
2016	170,503	9%	379	0.22%	671,155	56.5
2017	433,011	24%	904	0.21%	1,307,516	69.1
2018	394,774	22%	688	0.17%	842,728	81.6
2019	494,685	27%	539	0.11%	580,092	92.9
2020	199,155	11%	186	0.09%	73,388	253.4

Screening group						
Birth Registry	114,560	6%	102	0.09%	331,484	30.8
Blood Bank	187,295	10%	303	0.16%	778,103	38.9
Harm Reduction Network	13,114	1%	18	0.14%	27,843	64.6
Inpatient	239,624	13%	570	0.24%	684,593	83.3
NCDC	162,061	9%	324	0.20%	459,197	70.6
Outpatient clinics	987,046	54%	1434	0.15%	1,491,207	96.2
Prisoners	8,770	0%	71	0.81%	30,687	231.4
Military recruits	24,200	1%	46	0.19%	82,980	55.4
Tbilisi city hall	25,795	1%	41	0.16%	115,288	35.6
Missing	66,343	4%	254	0.38%	210,945	120.4
Region of the first screening						
Tbilisi	815,350	45%	1576	0.19%	2,209,702	71.3
Other	980,407	54%	1492	0.15%	1,907,664	78.2
Missing	33,051	2%	95	0.29%	94,960	100.0
At least one positive anti-HCV test						

	Yes	120,791	7%	664	0.55%	364,830	182.0
	No	1,708,017	93%	2499	0.15%	3,847,496	65.0
Conversion of anti-HCV test results							
	Yes	17,323	1%	133	0.77%	56,449	235.6
	No	1,811,485	99%	3030	0.17%	4,155,878	72.9

Abbreviations: TB, tuberculosis; HCV, hepatitis C virus; PY, person-years; IR, incidence rate; Anti-HCV, antibodies against hepatitis C virus.

Table 3.2. Unadjusted Incidence rates of newly diagnosed active TB by HCV infection status (per 100,000 person-years)

Group	N	TB cases	PY	IR (95% CI)	IRR 95% CI
Never infected with HCV (HCV antibody-negative)	1,708,017	2,499	3,847,497	65.0 (62.4, 67.6)	1
Untreated HCV infection*	70,341*	305	102,993	296.1 (263.8, 331.3)	4.6 (4.0, 5.1)
Treated HCV infection	53,456	165	151,232	109.1 (93.1, 127.1)	1.7 (1.4, 2.0)
HCV cured (subset of treated)	43,573	116	117,003	99.1 (81.9, 118.9)	1.5 (1.3, 1.8)
Anti-HCV-positive/Viremia negative	15,921	84	59,607	140.9 (112.4, 174.5)	2.2 (1.7, 2.7)
Anti-HCV-positive/Viremia missing	21,277	110	50,998	215.7 (177.3, 260.0)	3.3 (2.7, 4.0)

*Includes both treated and untreated individuals because those treated contributed some person-time to the untreated group.

Abbreviations: TB, tuberculosis; HCV, hepatitis C virus; PY, person-years; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval; Anti-HCV, antibodies against hepatitis C virus.

Table 3.3. Multivariable models assessing association between HCV infection status and active tuberculosis. Adults tested for anti-HCV between January 1, 2015 and September 30, 2020. (N=1,778,383)

HCV category	**aHR (95% CI)***				
	Main model without IPW	**Main model with IPW**	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3
Never infected with HCV	1	1	1	1	1
Treated HCV	1.7 (1.4, 2.0)	1.6 (1.4, 2.0)	1.7 (1.4, 2.1)	1.6 (1.4, 2.0)	1.5 (1.2, 1.8)
Untreated HCV	2.9 (2.4, 3.4)	2.9 (2.4, 3.4)	2.9 (2.5, 3.4)	2.9 (2.4, 3.4)	3.0 (2.5, 3.6)

*Adjusted for sex, municipality, and imprisonment.

Abbreviations: HCV, Hepatitis C Virus; aHR, adjusted hazards ratio; CI, confidence interval; IPW, inverse-probability weighting.

Table 3.4. Parameters and results of quantitative bias analysis for unmeasured confounder – injection drug use.

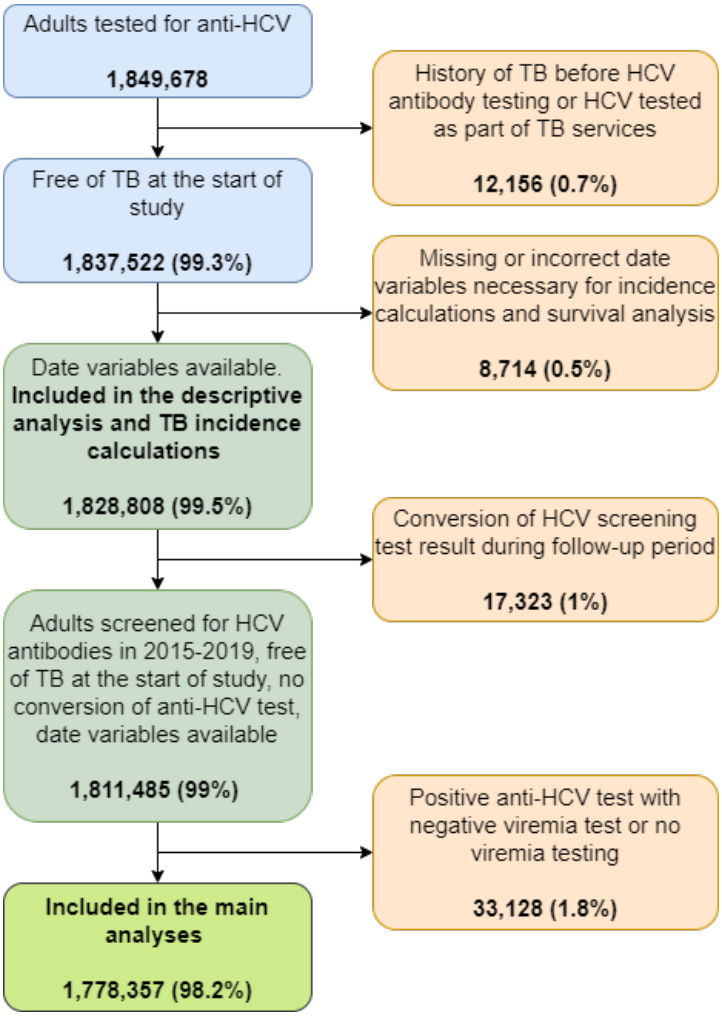
Parameter	Parameter values	Sensitivity analyses for P parameters				Sensitivity analyses for U parameter			
		SA 1	SA 2	SA 3	SA 4	SA 1	SA 2	SA 3	SA 4
Bias parameters									
Prevalence of IDU among HCV-negative **(P1)**	0.018	0.02	0.017	0.015	0.013	0.018	0.018	0.018	0.018
Prevalence of IDU among untreated HCV **(P2)**	0.2	0.18	0.22	0.24	0.26	0.2	0.2	0.2	0.2
Prevalence of IDU among treated HCV **(P3)**	0.24	0.22	0.26	0.28	0.3	0.24	0.24	0.24	0.24
Effect of IDU on rate of active TB on HR scale **(U)**	3	3	3	3	3	2.6	2.8	3.2	3.4
Observed estimates from the main model									
Estimated aHR (untreated vs uninfected)	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9
Estimated aHR (treated vs uninfected)	1.7	1.7	1.7	1.7	1.7	1.6	1.6	1.6	1.6
Bias factor*									
Bias factor (untreated vs uninfected)	1.35	1.31	1.39	1.44	1.48	1.28	1.32	1.39	1.42
Bias factor (treated vs uninfected)	1.43	1.38	1.47	1.51	1.56	1.35	1.39	1.47	1.51
Bias-adjusted model parameters**									
Bias-adjusted aHR (untreated vs uninfected)	2.15	2.22	2.08	2.02	1.96	2.26	2.20	2.09	2.04
Bias-adjusted aHR (treated vs uninfected)	1.19	1.23	1.16	1.12	1.09	1.26	1.23	1.16	1.13

Abbreviations: SA, sensitivity analysis; IDU, injection drug use; HCV, hepatitis C virus; aHR, adjusted hazards ratio

*Calculated with the following formula: $\frac{1+(U-1)*P_i}{1+(U-1)*P_1}$, where i=2,3 for untreated and treated groups.

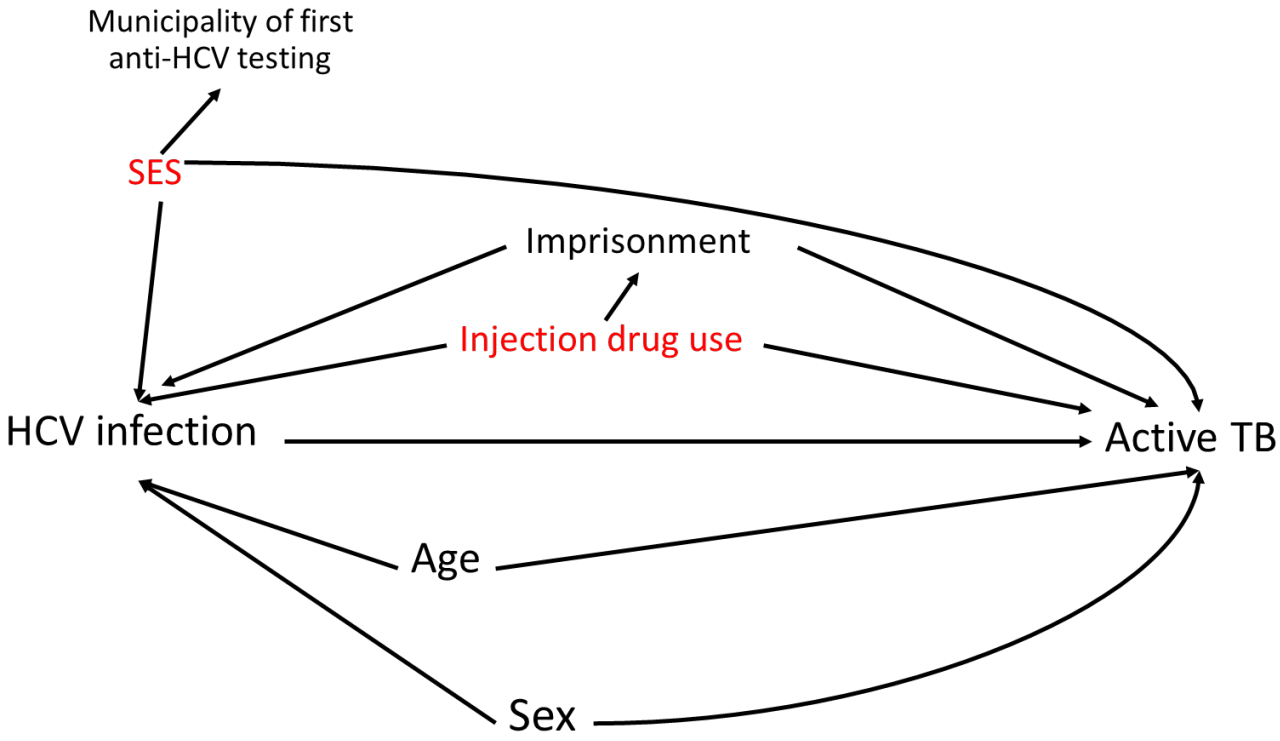
** The bias-adjusted hazards ratio was derived by dividing the observed aHR by the bias factor

Figure 3.1. Flow chart of selecting the study population - persons tested for anti-HCV, January 1, 2015 - September 30, 2020



Abbreviations: HCV, hepatitis C virus; TB, tuberculosis;

Figure 3.2. A directed acyclic diagram (DAG) of factors involved in a causal relationship of HCV infection and active TB.



Abbreviations: HCV, hepatitis C virus; TB, tuberculosis; SES, Socioeconomic status

Notes: SES and injection drug use are unmeasured confounders. The municipality is considered a proxy for the SES. Thus, the model was adjusted for it.

Supplemental material for chapter 3

Appendix 3.1. Detailed description of the study population selection.

To select the study population, after cleaning the dataset of the screening registry and only keeping the observations with the National ID is available (N=2,166,439), we started excluding groups based on the exclusion criteria.

1. First, we excluded the persons with age less than 18 at the time of their first anti-HCV testing (n=316,761 (15%)).

2. Next, to make sure that the cohort consists of persons free of the outcome of interest at the start of follow-up, I excluded the individuals with some evidence of TB before or at the time of their anti-HCV testing (n=12,130). These included three groups:

a. People who had TB diagnosis, with diagnosis date earlier than their first anti-HCV testing;

b. People who had TB diagnosis date later than their anti-HCV testing, but their TB case definition was not “new case” (i.e. they could have had first TB diagnosis before 2015);

c. People who had the determination of “TB program beneficiaries” on the variable of “HCV screening Target group.” These include people who had their first anti-HCV testing done as part of the investigation for TB diagnosis, i.e. they are either patients with confirmed TB diagnosis or with possible TB.

3. Next, we excluded 8,714 observations who had missing or conflicting entries on the date variables necessary for the incidence calculations and survival analysis: date of anti-HCV testing and date of death.

a. The remaining 1,828,834 individuals comprise the population who was included in the descriptive analysis and incidence calculations.

4. To come up with the final study population to include the multivariable analysis, we also excluded persons in which the definitive classification of exposure of interest is challenging. These included the two groups:

a. We first excluded the 17,323 individuals who had conversion of anti-HCV testing result.

b. Next, we excluded persons with positive anti-HCV test result who did not undergo viremia testing (n=17,207) because it is impossible to classify them into any of the exposure categories. We also excluded those with negative result on viremia testing (n=15,921). In this group, we are unable to determine whether they had a false-positive antibody test result, previous hepatitis C treatment and cure before elimination program or outside the country, or spontaneous clearance after initial HCV exposure and infection. Therefore, their exposure status also cannot be classified.

The steps described above resulted in the final study population of 1,778,383 individuals included in the survival analysis models.

Appendix 3.2. Quantitative bias analysis for unmeasured confounder – injection drug use.

1. Deriving the number of people who inject drugs by exposure categories

A national estimate for injection drug use in 2016 was 52,500 (2.24% of the population aged 18-64).[182] According to the MMWR article (Stvilia et al., 2019), 40.5% of injection drug users enrolled in Georgian Harm Reduction services were antibody positive.[119] We can further assume that 84% of them had active HCV infection, of which 75.1% started treatment and 86.7% completed treatment. If we extrapolate those numbers to the whole population of people who inject drugs, we can derive the following estimates:

40.5% of 52,500 PWIDs are anti-HCV positive – 21,263 PWIDs, of whom 17,861 had active HCV infection. Of those, 65% can be estimated as completed treatment (17,861*0.751*0.867), which gives us 11,630 individuals treated for hepatitis C and 6,231 with untreated hepatitis C.

2. Calculating the proportion of PWIDs in each of the exposure categories:

If we assume that 40.5% of PWIDs are anti-HCV positive, then we can estimate 59.5% of injection drug users (n=31,238) to be anti-HCV negative, which comprises 1.829% of our 1,708,041 HCV-negative individuals in the study population.

In our sample, 38.6% of person-time was in the untreated category. Therefore, to calculate the proportion of PWIDs in each of the HCV-positive groups, we can split 79,514 individuals with positive viremia into 30,708 untreated and 48,806 treated individuals. Therefore, the proportion of PWIDs among the treated group can be estimated as

11630/48806=23.83% and the proportion of PWIDs among the untreated group can be estimated as 6231/30708=20.29%

We can assume that the portion of PWID who uses harm reduction services are likely at less risk of HCV infection due to uptake of the harm reduction services. Therefore, the estimate of 40.5% and all the subsequent calculations that rely on that number is underestimated. To address this, we conducted a sensitivity analysis of bias analysis and ranged the bias analysis parameters to see how sensitive the final estimates are to the assumed values of the parameters.

Chapter 4: All-cause mortality and TB recurrence among patients successfully treated for TB: the role of HCV coinfection

Abstract

Introduction: Despite the frequent overlap of tuberculosis (TB) and hepatitis C disease, the impact of hepatitis C coinfection on long-term outcomes of patients with TB is not well understood. In this study, we sought to assess the effect of hepatitis C coinfection on all-cause mortality and TB recurrence among patients successfully treated for TB in the country of Georgia.

Methods: We conducted a population-based cohort study in Georgia among adult patients with newly diagnosed TB who successfully completed their TB treatment. We used data from the nationwide electronic databases of the National TB Program, Hepatitis C Elimination Program, and National Death Registry. The primary exposure of interest was hepatitis C status with three categories: uninfected, infected but untreated, and treated. The outcomes of interest were all-cause mortality and recurrence of TB. We calculated all-cause mortality and TB recurrence rates by different demographic factors and by exposure status. We used Cox proportional hazards regression models using age as a time-scale to calculate adjusted hazards ratios (aHR) and 95% confidence intervals.

Results: Among 7,850 patients with a successful TB treatment outcome, The age- and sex-standardized mortality ratio (SMR) was 2.17 (95% CI: 1.9, 2.5) compared to the general population. Complete hepatitis C status was available in 5,818 (74%) persons.

There was no strong evidence of an association between treated or untreated hepatitis C coinfection and mortality in drug-susceptible (DS) or drug-resistant (DR) TB group. Untreated hepatitis C was associated with increased hazards of TB recurrence in both patients with DS TB (aHR= 1.6, 95%CI: 1.0, 2.4) and DR TB (aHR=3.4, 95%CI: 0.6, 18.2).

Conclusion: We found that persons who were successfully treated for TB had more than twice the mortality compared to the general population, and patients with untreated HCV coinfection had a higher rate of TB recurrence. Our findings suggest that improving the post-treatment follow-up and care after TB treatment completion should be explored as a potential mechanism to improve the long-term health outcomes in patients with TB; treatment of hepatitis C among patients with TB may decrease the risk of TB recurrence.

Introduction

Over the past decade, tuberculosis (TB) was the leading cause of death due to a single infectious agent before the onset of the COVID-19 pandemic. Each year, an estimated 10 million people develop active TB disease, and 1.4 million people die due to TB.[1] However, the estimated mortality from TB includes the people with TB who die before or during TB treatment, while death and other long-term consequences after treatment completion are not included in these estimates and are scarcely studied.[23] Like TB, hepatitis C virus (HCV) infection is one of the most common infectious diseases globally, with an estimated 58 million people living with hepatitis C and 290,000 deaths attributable to it in 2019. HCV coinfection is common among patients with TB; the prevalence of HCV coinfection among patients with newly diagnosed TB varies widely by country and ranges from 2% to 27%.[129] Despite frequent overlap, the role of hepatitis C coinfection in the long-term outcomes of patients with TB has been poorly understood.

Patients treated for TB have 3-4 times higher mortality compared to the general population.[50,51] Death may be caused by active disease or by pulmonary and extrapulmonary sequelae of TB, such as lung impairment and cardiovascular complications.[50-54] Some studies suggest that liver disease is a more frequent cause of death among patients cured of TB than in the general population.[51] More thorough evidence about the role of specific liver diseases, such as hepatitis C, is lacking. Patients with TB and HCV coinfection are at a 3-times higher risk of hepatotoxicity due to anti-TB drugs than HCV-negative patients with TB.[36,38] This combined effect of TB drugs and HCV infection can cause long-term impairment of liver function and could be one of the factors explaining high mortality after TB treatment.[51]

Another challenge in TB control is a recurrence of TB after successful treatment completion, which requires retreatment of a patient.[39] Recurrence can occur via two mechanisms: (1) Endogenous relapse, i.e., repeated episode of TB caused by regrowth of the same strain of *Mycobacterium tuberculosis* (*Mtb)* that caused the initial TB episode, or (2) Exogenous reinfection with a new *Mtb* strain.[39,41] Distinguishing relapse from reinfection may be challenging and requires genotypic analysis to determine whether the recurrent episode of TB is caused by the original Mtb isolate or due to infection and disease with a new strain of Mtb.[41] Rates of and reasons for recurrence vary widely between countries.[39] Some of the factors universally associated with TB recurrence are HIV infection, malnutrition, diabetes, renal and liver failure, and substance abuse.[40] All of these are immunosuppressive conditions, which highlight the critical role of host immunity in the recurrence of TB.[39] However, it is not known if HCV infection also increases the risk of TB recurrence by disrupting immune response against *Mtb*.[134]

The Eastern European country of Georgia (population ~3.7 million) has a high TB burden. It is designated as a high-priority country for TB control in the WHO European Region, with an estimated incidence of 74 cases per 100,000 population in 2019.[1,55] The National TB Program (NTP) provides universal coverage of TB diagnostic and treatment services countrywide, and all clinical data is stored in a nationwide electronic database. The prevalence of chronic HCV infection is also very high in Georgia, affecting 5.4% of the general adult population (~150,000 individuals) based on 2015 prevalence estimates.[183] In 2015, Georgia initiated the world's first formal nationwide hepatitis C elimination program, which provides free hepatitis C testing and treatment for all citizens.[113-115] The country integrated hepatitis C screening into multiple existing health programs and

settings, including the National TB Program.[114,116-119] Patients diagnosed with HCV infection are treated with new directly acting antiviral agents (DAAs).[115] Diagnostic and treatment data from both the Georgian NTP and hepatitis C elimination programs are collected in nationwide electronic databases.[116,175]

The objective of this study was to assess the effect of HCV coinfection on all-cause mortality and TB recurrence among patients successfully treated for TB in Georgia. The prespecified hypothesis was that mortality and TB recurrence rates after TB treatment completion are higher among patients with TB and HCV coinfection than those with only TB disease. Large electronic datasets available in Georgia and the ongoing hepatitis C elimination program provide a unique opportunity to study the impact of HCV coinfection on long-term outcomes among patients with TB. Our findings provide evidence for additional post-treatment management and monitoring of coinfected patients who complete TB treatment and can help improve the long-term outcomes in this population.

Methods

Study design and participants

We conducted a cohort study among adult patients (≥18 years of age) with newly diagnosed TB in 2015-2019 who successfully completed TB therapy. The follow-up period ended on September 30, 2020. Patients with unsuccessful or unknown TB treatment outcomes were excluded from the analysis. Patients with indeterminate hepatitis C status were retained in overall standardized mortality ratio calculations but excluded from the further analyses. Exclusion criteria were: (1) unknown anti-HCV antibody test results or

conversion of the result during the follow-up period; (2) positive anti-HCV antibody test results with negative or missing HCV viremia results.

Data sources

We constructed the cohort of patients with TB from the TB surveillance database managed by the Georgian National Center for Tuberculosis and Lung Diseases (NCTLD). The National TB surveillance database includes clinical and TB treatment-related information on every patient enrolled in Georgia's National TB Program (NTP). NTP provides free-of-charge diagnosis and treatment for TB countrywide. We cross-linked the TB surveillance database with the national death registry using the national ID number, and if a patient was found to be deceased, we extracted the date of death.

We obtained hepatitis C testing and treatment information from two nationwide electronic databases: the national hepatitis C screening registry and hepatitis C elimination program clinical database "Elimination C" (ElimC). The screening registry is a real-time, nationwide web-based system managed by the National Center for Disease Control and Public Health (NCDC). The screening registry collects data from all stakeholders providing hepatitis C screening with antibody testing throughout Georgia, including blood banks, antenatal care clinics, hospitals, outpatient clinics, harm-reduction centers, and NCDC with its regional laboratory network. ElimC is a nationwide web-based database that collects information from all clinics providing HCV diagnostic and treatment services to patients enrolled in the HCV elimination program. ElimC includes data on every individual who underwent confirmatory viremia testing after a

positive HCV antibody test in the elimination program.

The linking variable between all sources of data was the national ID number. This unique identifier is assigned to every citizen of Georgia and is recorded in all data sources described above.

Variables and definitions

We extracted the following variables from the TB surveillance database: (1) Socio-demographic variables, such as sex, age, date of birth, region of residence, employment status, internal displacement status, and history of imprisonment; (2) TB-related diagnostic and treatment variables, such as date of diagnosis, treatment initiation and completion dates, treatment regimen (first-line or second-line), whether a case was new or previously treated, treatment outcome, and subsequent diagnosis of TB after successful completion of the first treatment episode. From hepatitis C databases, we extracted anti-HCV antibody testing and viremia testing dates and results, hepatitis C treatment initiation and completion status, and date of hepatitis C treatment completion.

For inclusion in the study population, patients were defined as successfully treated for TB if their treatment outcome was determined to be "cure" or "completed treatment" by the NTP per WHO definitions.[23] Patients were defined as having drug-resistant (DR) TB if they were enrolled in second-line TB treatment and as drug-susceptible (DS) TB otherwise. For the incidence rate and survival analyses calculations, we defined the baseline date as the first TB treatment completion date. We made two assumptions about the baseline date: (1) In patients with DS TB with a missing treatment completion date,

we assumed they were on a standard 6-month regimen and imputed the treatment completion date by adding 180 days to the date of diagnosis.[25] We could not make a similar assumption for the patients with DR TB since the duration of second-line treatment regimens was highly variable during the study period.[184] Therefore, patients with a missing date of second-line treatment completion were excluded from the analysis; (2) for the patients that had the first anti-HCV antibody testing performed after the TB treatment completion, we assumed that the hepatitis C status was the same at the time of TB treatment completion. Hence, we set the baseline date at the TB treatment completion date.

The primary exposure of interest was hepatitis C status, which was defined as "uninfected" if a patient's anti-HCV antibody test result was negative, "untreated" if a patient had positive HCV viremia result without completing treatment for hepatitis C, and "treated" if a patient completed their most recent hepatitis C treatment course with DAAs within the elimination program.

The first outcome of interest was all-cause mortality. The second outcome of interest was TB recurrence, defined as a second episode of active TB diagnosis (clinical or laboratory-confirmed) after successfully completing the first TB treatment. TB recurrence cases included both (endogenous) relapse cases and new episodes of TB caused by reinfection.[23] Due to the lack of genotypic data, we could not distinguish between these two mechanisms of recurrence.

Statistical analysis

We calculated the age- and sex-standardized mortality ratio (SMR) for the overall cohort of all TB patients, irrespective of HCV status. Reference rates for SMR calculation were obtained from 2019 mortality data on the general population in the country of Georgia.[185] Since the reference age-specific rates were available in 5-year categories, we only included patients aged 20 and above and excluded adults aged 18 and 19.

In patients with hepatitis C status available, we calculated the TB recurrence and all-cause mortality rates by sex, employment status, region of residence and other socio-demographic factors, as well as within three exposure groups based on hepatitis C status: uninfected, untreated, and treated. We calculated the person-time by counting the number of days from the baseline date to the first occurrence of either outcome of interest (death or TB recurrence) or the end of the study period (September 30, 2020).

We used Cox proportional hazards regression models to calculate adjusted hazards ratios (aHR) and 95% confidence intervals with robust standard errors for the parameter estimates. The models used age as a time scale. In the TB recurrence models, death was treated as a competing event, and the proportional hazards model for the subdistribution of a competing risk (Fine and Gray approach) was used.[186,187] We selected potential confounders for inclusion in the model based on directed acyclic graph theory (figure 1).[167] We adjusted both, mortality and recurrence models for the following variables: sex, employment status (employed, unemployed or military), place of TB diagnosis (capital city Tbilisi, other regions, or penitentiary system), whether a person was internally displaced from the occupied regions, and presence of HIV infection.

Hepatitis C status was treated as a time-varying variable in incidence calculations and all

multivariable models. Treated individuals contributed follow-up time to the untreated group until completing the hepatitis C treatment, at which point they moved to the treated group. If a person completed hepatitis C treatment before their TB treatment completion, they were included in the "treated" group for the whole follow-up time. All analyses for both outcomes were stratified on drug-susceptibility status because treatment regimens, duration, effectiveness, and various other factors are highly different between patients with DS and DR TB.

Sensitivity analysis

We conducted several sensitivity analyses to explore the potential impact of our assumptions about the baseline date. For this purpose, we ran three additional multivariable models with the study population's varying assumptions and selection process. In the first sensitivity analysis model, we only used observations for which the hepatitis C status was known by their TB treatment completion. In the second model, we did not impute the TB treatment completion date and excluded the patients with this variable missing. In the third model, we combined the two above-mentioned restrictions and retained in the analysis only observations with known HCV status by the time of treatment completion and known date of treatment completion.

Ethics

The study was approved by the Institutional Review Boards (IRBs) at Emory University,

NCTLD, and NCDC.

Results

Description of study participants

Among 9,610 adults newly diagnosed with TB between 2015-2019, 1,760 (18.3%) had unsuccessful or unknown TB treatment outcomes. Among the remaining 7,850 patients, complete hepatitis C status was available in 5,818 (74%) persons, who were retained in the final analysis (Figure 2). Comparing patients with and without known hepatitis C status did not identify any meaningful differences in most demographic or clinical factors. However, patients with DR TB and those who completed TB treatment in recent years were more likely to have the hepatitis C status available (Table 1).

The majority of the study population included in the final analyses were males (3,723, 64%). The median age was 40 years (Q1-Q3: 29-55). The large majority of the study population was unemployed (4,644, 80%), 77 (1%) were diagnosed with TB in the penitentiary system, and 236 (4%) had previously been incarcerated. Most of the study population had DS TB (5,382, 93%), with only 436 patients (7%) being on treatment for DR TB (Table 1).

All-cause mortality

Among patients who successfully completed treatment for active TB aged 20 and above

(n=7,585), there were 438 (5.8%) deaths, of which 182 occurred during the first year of follow-up. The age- and sex-standardized mortality ratio (SMR) for persons who successfully completed TB treatment was 2.17 (95%CI: 1.9, 2.5) compared to the mortality rate in the general population.

Among 5,374 patients who successfully completed treatment for DS TB and had hepatitis C status available, the median follow-up after TB treatment completion was 28 months, with a total of 13,498 person-years accrued. Among this cohort, we identified 261 (4.9%) deaths due to any cause, which equated to the overall all-cause mortality rate of 1,934 (95%CI 1,709, 2,179) per 100,000 person-years. Among different subgroups, we observed a higher all-cause mortality rate among males compared to females (mortality rate ratio, MRR=2.4, 95%CI: 1.8, 3.2), unemployed persons compared to employed (MRR=3.0, 95%CI: 1.8, 5.1), and among people with untreated hepatitis C compared to those never infected (MRR=1.5, 95%CI: 1.0, 2.4) (Table 2).

Among 436 patients with DR TB who successfully completed TB treatment, the median follow-up was 23 months, with a total of 853 person-years accrued. We identified 18 (4.1%) patients who died after successful TB treatment completion, which equated to an all-cause mortality rate of 2,111 (95%CI: 1,251, 3,337) per 100,000 person-years. Due to the low numbers in the DR TB group, we could not obtain subgroup-specific mortality rates with high precision among different demographic and exposure groups (Table S1).

In multivariable analysis, we could not find strong evidence of an association between treated hepatitis C and all-cause mortality among DS TB patients (aHR=0.4, 95%CI: 0.2, 1.1) or DR TB patients (aHR=1.5, 95%CI: 0.4, 6.4). Untreated hepatitis C also was not

associated with all-cause mortality in either of the groups (Table 3).

TB recurrence

Among 5,351 patients who were successfully treated for DS TB, the median follow-up was 28 months, with a total of 12,916 person-years accrued. We identified 262 (4.9%) cases of TB recurrence, which equated to the overall recurrence rate of 2,029 (95%CI: 1,790, 2,290) cases per 100,000 person-years. Median time from TB treatment completion to recurrence was approximately 10 months (Q1-Q3: 5-18 months). Among different subgroups, a higher recurrence rate was observed among males compared to females (Incidence rate ratio, IRR=1.6, 95%CI: 1.2, 2.1), those with a history of incarceration (IRR=2.3, 95%CI: 1.5, 3.6), and among people with untreated hepatitis C compared to those never infected (IRR=2.3, 95%CI: 1.6, 3.3) (Table 4).

Among 435 patients successfully treated for DR TB, the median follow-up was 22 months, with a total of 832 person-years accrued. We identified 10 cases (2.3%) of TB recurrence after successful treatment completion, which equated to the recurrence rate of 1,202 (95%CI: 611, 2142) cases of recurrence per 100,000 person-years. Due to the low number of cases, we were not able to obtain subgroup-specific recurrence rate with high precision among different demographic and exposure groups (Table S2)

In multivariable analysis, we could not find a strong evidence of association between hepatitis C and TB recurrence among DS TB patients (aHR=0.6, 95%CI: 0.3, 1.3) or DR TB patients (aHR=1.4, 95%CI: 0.4, 5.3). Untreated hepatitis C was associated with increased risk of TB recurrence in both patients with DS TB (aHR= 1.6, 95%CI: 1.0, 2.4)

and DR TB (aHR=3.4, 95%CI: 0.6, 18.2), although the estimate in the DR TB group has very low precision.

Sensitivity analysis

We performed three sensitivity analysis models for each analytic group (DS and DR TB) and outcome of interest (all-cause mortality and TB recurrence). Overall, the models that only excluded the patients with imputed date TB treatment completion (i.e., sensitivity analysis model 2) did not change the parameter estimates meaningfully. However, the models that excluded the patients diagnosed with hepatitis C after their TB treatment completion (i.e., sensitivity analyses models 1 and 3) caused some fluctuation in parameter estimates in most analyses. Specifically, in sensitivity analysis models 1 and 3 association between untreated hepatitis C and TB recurrence among patients with DS TB changed from negative to weak positive. Association between untreated hepatitis C and TB recurrence among the DS TB group remained stable (aHR=1.6) in all sensitivity analysis models. However, precision was reduced due to the smaller sample size (Tables 3 and 5).

Discussion

In this population-based cohort study, we used population-based databases in the country of Georgia to explore the post-treatment outcomes among patients successfully treated for TB and to evaluate the impact of hepatitis C on these outcomes. We found that all-

cause mortality among patients who were successfully treated for TB was more than twice that than in the general population. Patients who completed treatment for DS TB who had chronic hepatitis C coinfection but had not undergone HCV treatment were at increased risk for TB recurrence. However, there was no association between hepatitis C status and all-cause mortality. Due to the low sample size of patients with DR TB, we could not reliably assess the effect of hepatitis C on long-term outcomes in this group. Our findings provide additional explanation for the potential contributing factors of TB recurrence, which is a major challenge for TB control, and provide a groundwork for further studies in Georgia to explore the post-treatment health outcomes in patients with TB.

Georgia has a high post-treatment mortality among MDR and XDR TB patients lost to follow-up from treatment (all-cause mortality rate of 5,100 per 100,000).[58,59,62] However, post-treatment mortality among successfully treated patients with TB has not been previously evaluated. We found that all-cause mortality is higher among patients who had completed TB therapy compared to the general population, even in patients with successfully treated DS TB during the first 2-3 years after the treatment completion. This finding aligns with the existing literature, which suggests that even after successful treatment completion, patients with TB have higher mortality than the general population.[50,51] However, we did not find an association between all-cause mortality after TB treatment and hepatitis C status.

A novel finding of our study is that patients with DS TB who successfully completed TB therapy were more likely to have a recurrence of TB if they have untreated HCV coinfection compared to those without hepatitis C. Our data do not allow us to make a definitive claim whether this association is causal. Even though we carefully examined the

potential confounders and adjusted for the factors that might confound this association, some unmeasured socio-behavioral factors may explain this association, such as low socioeconomic status and injection drug use, both of which can be causes of hepatitis C and TB recurrence. However, the causal nature of this association is biologically plausible. HCV has immunosuppressive effects that might interfere with mechanisms responsible for the immune response against TB and hinder Mtb eradication.[132,134,135,141,142,145,146] This might have a negative effect even after TB treatment, causing reactivation of the same strain of TB and relapse, which would be reflected in the higher rate of TB recurrence compared to persons without HCV infection.

Our study had several limitations: (1) in the TB surveillance dataset, drug susceptibility testing was not available on all patients; however, we were able to infer drug-resistance status by treatment regimens. Therefore, we made DS vs. DR TB determination based on the treatment regimens; (2) we could not conduct active follow-up on patients after TB treatment completion and relied on the existing databases to ascertain the long-term outcomes, TB recurrence and death. Therefore, estimated rates of mortality and recurrence in our analyses might be underestimated. However, the national TB surveillance dataset includes all patients diagnosed within NTP, which provides free TB diagnostic and treatment services countrywide. Therefore, the proportion of patients diagnosed outside NTP can be considered negligible. Death registry also has high accuracy in capturing the deaths nationwide, with an estimated sensitivity exceeding 95%;[188] (3) Our mortality data did not include reasons of death. Hence, our analysis focused on all-cause mortality instead of cause-specific mortality; (4) Due to a lack of genotypic data, we could not determine whether TB recurrence cases were developed

through relapse or reinfection. However, we hypothesize that majority of cases were due to relapse, not reinfection. A genotypic study among MDR TB patients in Georgia found that 83% of recurrence cases occurred due to relapse;[49] (5) We did not accrue a sufficient number of cases and person-time of follow-up among patients with DR TB to reliably estimate the recurrence and mortality rates in this group.

Despite these limitations, this study has important strengths and implications. First, this is the largest population-based cohort in Georgia assessing the long-term outcomes among patients who successfully completed TB treatment, and the first of its kind to assess these outcomes in patients with DS TB. Previous studies focused on mortality in subpopulations of DR TB patients, such as those lost to follow-up or who had XDR TB.[58,59] Second, our study used nationwide databases that enable us to accumulate adequate sample size and follow-up time for studying rare outcomes such as death and recurrence. Additionally, these databases have been previously used for research purposes, and they demonstrated high accuracy and quality of data.[114,175,188] Third, our study established a cohort that can be further followed in the future with at least two new goals: (1) incorporate additional nationwide sources of data (e.g., hospital data, social service data), to evaluate other long-term outcomes of interest, such as morbidity and hospitalization due to long-term lung impairment and liver disease. (2) Increase the sample size and follow-up time, especially in patients with DR TB, to assess the outcomes in this group with higher precision.

In conclusion, in this population-based cohort study, we found that patients who had successfully been treated for TB had higher mortality than the general population. However, mortality did not differ by hepatitis C status. We also found that patients with

untreated HCV coinfection had a higher rate of TB recurrence. Our findings suggest that improving the post-treatment follow-up and care after TB treatment completion would benefit the long-term health outcomes in patients with TB. Future studies should focus on identifying reasons for death in patients with successful TB treatment, elucidate the mechanism of TB recurrence and assess other long-term outcomes.

Funding

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Table 4.1. Comparison of patients with TB with and without hepatitis C status available

CHARACTERISTICS	Total		Hepatitis C status known		Hepatitis C status unknown		Prevalence ratio (95% CI)
	N	%	N	%	N	%	
TOTAL COHORT	**7,850**	**100%**	**5818**	**74%**	**2,032**	**26%**	
Sex							
Male	5,135	65.4%	3723	72.5%	1,412	27.5%	1
Female	2,715	34.6%	2095	77.2%	620	22.8%	1.06 (1.04, 1.09)
Region (grouped)							
Tbilisi	3,773	48.1%	2742	72.7%	1,031	27.3%	1
Penitentiary system	99	1.3%	77	77.8%	22	22.2%	1.07 (0.96, 1.19)
Other	3,978	50.7%	2999	75.4%	979	24.6%	1.04 (1.01, 1.07)
Employment status							
Employed	1,277	16.3%	955	74.8%	322	25.2%	1
Unemployed	6,275	79.9%	4644	74.0%	1,631	26.0%	1.06 (0.84, 1.33)
Military	19	0.2%	15	78.9%	4	21.1%	0.99 (0.96, 1.02)
Missing	279	3.6%	204	73.1%	75	26.9%	-

History of imprisonment							
Yes	336	4.3%	236	70.2%	100	29.8%	0.95 (0.88, 1.01)
No	7,266	92.6%	5400	74.3%	1,866	25.7%	1
Missing	248	3.2%	182	73.4%	66	26.6%	-
Internally displaced person							
Yes	396	5.0%	298	75.3%	98	24.7%	1.02 (0.96, 1.08)
No	7,171	91.4%	5311	74.1%	1,860	25.9%	1
Missing	283	3.6%	209	73.9%	74	26.1%	-
Year of TB treatment completion							
2015	668	8.5%	368	55.1%	300	44.9%	1
2016	1,633	20.8%	980	60.0%	653	40.0%	1.09 (1.01, 1.18)
2017	1,813	23.1%	1265	69.8%	548	30.2%	1.27 (1.18, 1.37)
2018	1,617	20.6%	1277	79.0%	340	21.0%	1.43 (1.33, 1.54)
2019	1,434	18.3%	1304	90.9%	130	9.1%	1.65 (1.54, 1.77)

2020	685	8.7%	624	91.1%	61	8.9%	1.65 (1.54, 1.78)
Drug-susceptibility							
DS TB	7,338	93.5%	5382	73.3%	1,956	26.7%	1
DR TB	512	6.5%	436	85.2%	76	14.8%	1.16 (1.12, 1.21)
HIV status							
Positive	114	1.5%	76	66.7%	38	33.3%	0.89 (0.78, 1.02)
Negative	6,715	85.5%	5008	74.6%	1,707	25.4%	1
Missing	1,021	13.0%	734	71.9%	287	28.1%	-

Abbreviations: TB, tuberculosis; CI, confidence interval; HIV, Human Immunodeficiency Virus.

Table 4.2. All-cause mortality among patients who successfully completed treatment for DS TB.

CHARACTERISTICS	Total			All-cause deaths			
	N	%	PY	N	%	Mortality rate per 100,000 PY	Mortality rate ratio (95% CI)
TOTAL COHORT	**5374**	**100**	**13,498**	**261**	**4.9%**	**1,934 (1709, 2179)**	
Sex							
Male	3,437	64.0%	8,461	209	6.1%	2,470 (2,147, 2,829)	2.4 (1.8, 3.2)
Female	1,937	36.0%	5,037	52	2.7%	1,032 (771, 1,354)	1.0
Region (grouped)							
Tbilisi	2,514	46.8%	6,024	103	4.1%	1,710 (1,396, 2,074)	1.0
Penitentiary system	69	1.3%	137	0	0.0%	0	-
Other	2,791	51.9%	7,336	158	5.7%	2,154 (1,831, 2,517)	1.3 (1.0, 1.6)
Employment status							
Employed	858	16.0%	2,074	15	1.7%	723 (405, 1,193)	1.0
Unemployed	4,317	80.3%	10,956	240	5.6%	2,191 (1,922, 2,486)	3.0 (1.8, 5.1)
Military	13	0.2%	42	0	0.0%	0	-
Missing	186	3.5%	-	6	3.2%	0	-

Diagnosed with TB in penitentiary system							
Yes	69	1.3%	137	0	0.0%	0	-
No	5,305	98.7%	13,360	261	4.9%	1,954 (1,724, 2,206)	-
History of imprisonment							
Yes	212	3.9%	529	10	4.7%	1,890 (905, 3,477)	1.0 (0.5, 1.8)
No	4,995	92.9%	12,601	249	5.0%	1,976 (1,738, 2,237)	1.0
Missing	167	3.1%	-	2	1.2%	-	-
Internally displaced person							
Yes	276	5.1%	694	10	3.6%	1,441 (690, 2,650)	0.7 (0.4, 1.4)
No	4,917	91.5%	12,398	244	5.0%	1,968 (1,729, 2,231)	1.0
Missing	181	3.4%	-	7	3.9%	-	-
Year of TB treatment completion							
2015	368	6.8%	1,773	30	8.2%	1,692 (1,141, 2,416)	1.0

2016	957	17.8%	3,888	83	8.7%	2,135 (1,700, 2,646)	1.3 (0.8, 1.9)
2017	1,154	21.5%	3,607	64	5.5%	1,774 (1,366, 2,266)	1.0 (0.7, 1.6)
2018	1,162	21.6%	2,521	47	4.0%	1,864 (1,370, 2,479)	1.1 (0.7, 1.7)
2019	1,188	22.1%	1,445	30	2.5%	2,076 (1,401, 2,964)	1.2 (0.7, 2.0)
2020	545	10.1%	264	7	1.3%	2,652 (1,062, 5,463)	1.6 (0.7, 3.6)
HIV status							
Positive	68	1.3%	180	9	13.2%	5,000 (2282, 9492)	2.9 (1.5, 5.6)
Negative	4,585	85.3%	11,569	202	4.4%	1,746 (1,514, 2,004)	1.0
Missing	721	13.4%	-	50	6.9%	-	-
Hepatitis C status*							
Never infected	4,830	89.9%	12,041	230	4.8%	1,910 (1,671, 2,174)	1
Infected untreated	428	8.0%	779	23	5.4%	2,953 (1,871, 4,430)	1.5 (1.0, 2.4)
Infected treated	346	6.4%	626	8	2.3%	1,278 (550, 2,518)	0.7 (0.3, 1.4)

*Hepatitis C status was treated as a time-varying variable. Some patients who were treated contributed to the person-time to both treated and untreated group; therefore, total N in this variable sums up to more than the actual number of patients.

Abbreviations: DS TB, drug-susceptible tuberculosis; PY, person-year; CI, confidence interval; HIV,

Human Immunodeficiency Virus.

Table 4.3. Multivariable models assessing the association between hepatitis C status and all-cause mortality among persons with tuberculosis (TB) who had successfully completed therapy.

Hepatitis C status	**DS TB aHR (95% CI)***				**DR TB aHR (95% CI)***			
	Main model	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3	**Main model**	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3
Never infected	1	1	1	1	1	1	1	1
Infected, treated	0.4 (0.2, 1.1)	0.4 (0.1, 1.4)	0.4 (0.2, 1.1)	0.5 (0.1, 1.5)	1.5 (0.4, 6.4)	0.7 (0.1, 4.5)	1.5 (0.4, 6.4)	0.7 (0.1, 4.5)
Infected, untreated	1.0 (0.6 1.7)	0.6 (0.2, 1.5)	1.0 (0.6 1.8)	0.6 (0.2, 1.6)	1.0 (0.1, 8.1)	-	1.0 (0.1, 8.1)	-

* Adjusted for sex, employment status (employed, unemployed or military), place of TB diagnosis (region of residence or penitentiary system), whether a person was internally displaced from the occupied regions, and presence of HIV infection.

Abbreviations: DS TB, drug-susceptible tuberculosis; DR TB, drug-resistant tuberculosis; aHR, adjusted hazards ratio; CI, confidence intervals.

Table 4.4. Recurrence of TB among patients who successfully completed DS TB treatment

CHARACTERISTICS	Total			TB recurrence			
	N	% (col.)	PY	N	% (row)	Rate per 100,000 PY (95% CI)	Incidence rate ratio (95% CI)
TOTAL COHORT	**5,351**	**100**	**12,916**	**262**	**4.9%**	**2,029 (1790, 2,290)**	
Sex							
Male	3,420	63.9%	8,043	190	5.6%	2,362 (2,038, 2,723)	1.6 (1.2, 2.1)
Female	1,931	36.1%	4,872	72	3.7%	1,478 (1,156, 1,861)	1
Region (grouped)							
Tbilisi	2,501	46.7%	5,744	124	5.0%	2,159 (1796, 2574)	1
Penitentiary system	69	1.3%	129	6	8.7%	4,655 (1,700, 10,130)	2.2 (0.9, 4.6)
Other	2,781	52.0%	7,043	132	4.7%	1,874 (1,568, 2,223)	0.9 (0.7, 1.1)
Employment status							
Employed	854	16.0%	1,994	40	4.7%	2,006 (1,433, 2,731)	1
Unemployed	4,302	80.4%	10,471	214	5.0%	2,044 (1,779, 2,337)	1.0 (0.7, 1.4)

Military	13	0.2%	42	0	0.0%		
Missing	182	3.4%	0	8	4.4%		
Diagnosed with TB in penitentiary system							
Yes	69	1.3%	129	6	8.7%	4,655 (1,700, 10,130)	2.3 (1.0, 5.2)
No	5,282	98.7%	12,787	256	4.8%	2,002 (1,764, 2,263)	1
History of incarceration							
Yes	210	3.9%	484	22	10.5%	4,548 (2,849, 6,886)	2.3 (1.5, 3.6)
No	4,977	93.0%	12,079	234	4.7%	1,937 (1,697, 2,202)	1
Missing	164	3.1%		6	3.7%	-	-
Internally displaced persons							
Yes	274	5.1%	660	15	5.5%	2,272 (1,271, 3,748)	1.1 (0.7, 1.9)
No	4,900	91.6%	11,867	239	4.9%	2,014 (1,767, 2,286)	1
Missing	177	3.3%		8	4.5%	-	-
Year of TB treatment completion							

2015	365	6.8%	1,660	32	8.8%	1,928 (1,318, 2,721)	1
2016	954	17.8%	3,683	73	7.7%	1,982 (1,554, 2,492)	1.0 (0.7, 1.6)
2017	1,152	21.5%	3,450	75	6.5%	2,174 (1,710, 2,725)	1.1 (0.7, 1.7)
2018	1,156	21.6%	2,452	45	3.9%	1,835 (1,338, 2,455)	1.0 (0.6, 1.5)
2019	1,181	22.1%	1,409	36	3.0%	2,556 (1,790, 3,538)	1.3 (0.8, 2.1)
2020	543	10.1%	262	1	0.2%	381 (4, 2,121)	0.2 (0.03, 1.45)
HIV status							
Positive	66	1.2%	204	4	6.1%	1,961 (528, 5,020)	1.0 (0.4, 2.8)
Negative	4,572	85.4%	11,683	219	4.8%	1,875 (1,635, 2,140)	1
Missing	713	13.3%		39	5.5%	-	
Hepatitis C status*							
Never infected	4,810	89.9%	11,596	222	4.6%	1,914 (1,671, 2,184)	1
Infected, untreated	426	8.0%	727	32	7.5%	4,403 (3,011, 6,216)	2.3 (1.6, 3.3)
Infected treated	344	6.4%	593	8	2.3%	1,349 (581, 2,658)	0.7 (0.3, 1.4)

*Hepatitis C status was treated as a time-varying variable. Some patients who were treated contributed to the person-time to both treated and untreated groups; therefore, total N in this variable sums up to more than the actual number of patients.

Abbreviations: DS TB, drug-susceptible tuberculosis; PY, person-year; CI, confidence interval; HIV, Human Immunodeficiency Virus.

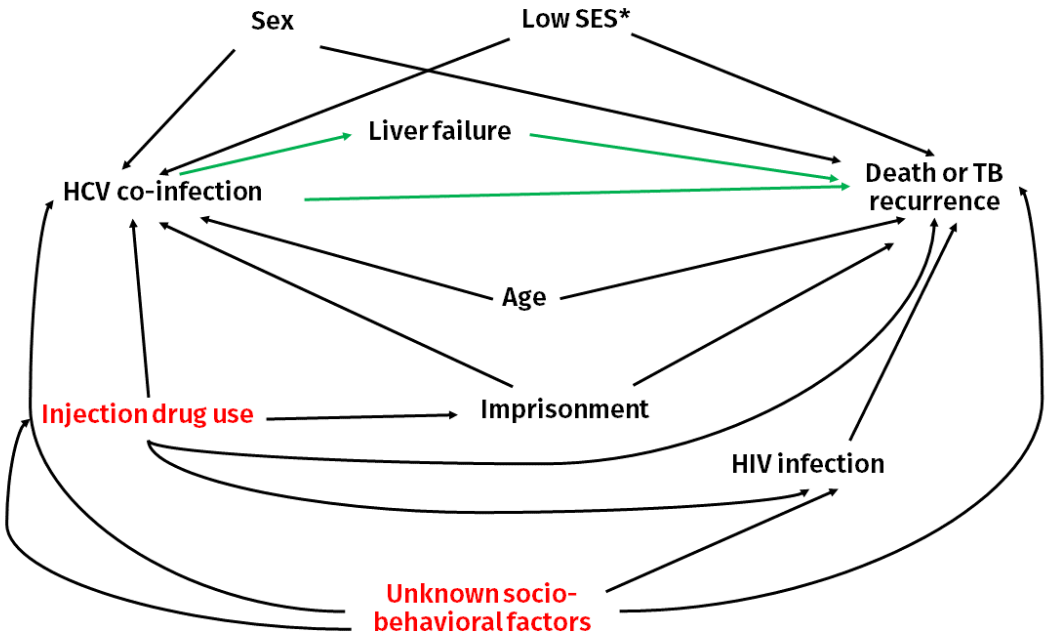
Table 4.5. Multivariable models assessing the association between HCV infection status and tuberculosis (TB) recurrence

Hepatitis C status	**DS TB**				**DR TB**			
	aHR (95% CI)*				**aHR (95% CI)***			
	Main model	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3	**Main model**	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3
Never infected	1	1	1	1	1	1	1	1
Infected treated	0.6 (0.3, 1.3)	1.1 (0.5, 2.3)	0.6 (0.3, 1.3)	1.1 (0.5, 2.4)	1.4 (0.4, 5.3)	4.2 (0.5, 33.8)	1.4 (0.4, 5.3)	4.2 (0.5, 33.8)
Infected untreated	1.6 (1.0, 2.4)	1.6 (0.8, 3.2)	1.6 (1.0, 2.5)	1.6 (0.8, 3.2)	3.4 (0.6, 18.2)	5.3 (0.5, 51.5)	3.4 (0.6, 18.2)	5.3 (0.5, 51.5)

* Adjusted for sex, employment status (employed, unemployed or military), place of TB diagnosis (region of residence or penitentiary system), whether a person was internally displaced from the occupied regions, and presence of HIV infection.

Abbreviations: DS TB, drug-susceptible tuberculosis; DR TB, drug-resistant tuberculosis; aHR, adjusted hazards ratio; CI, confidence intervals.

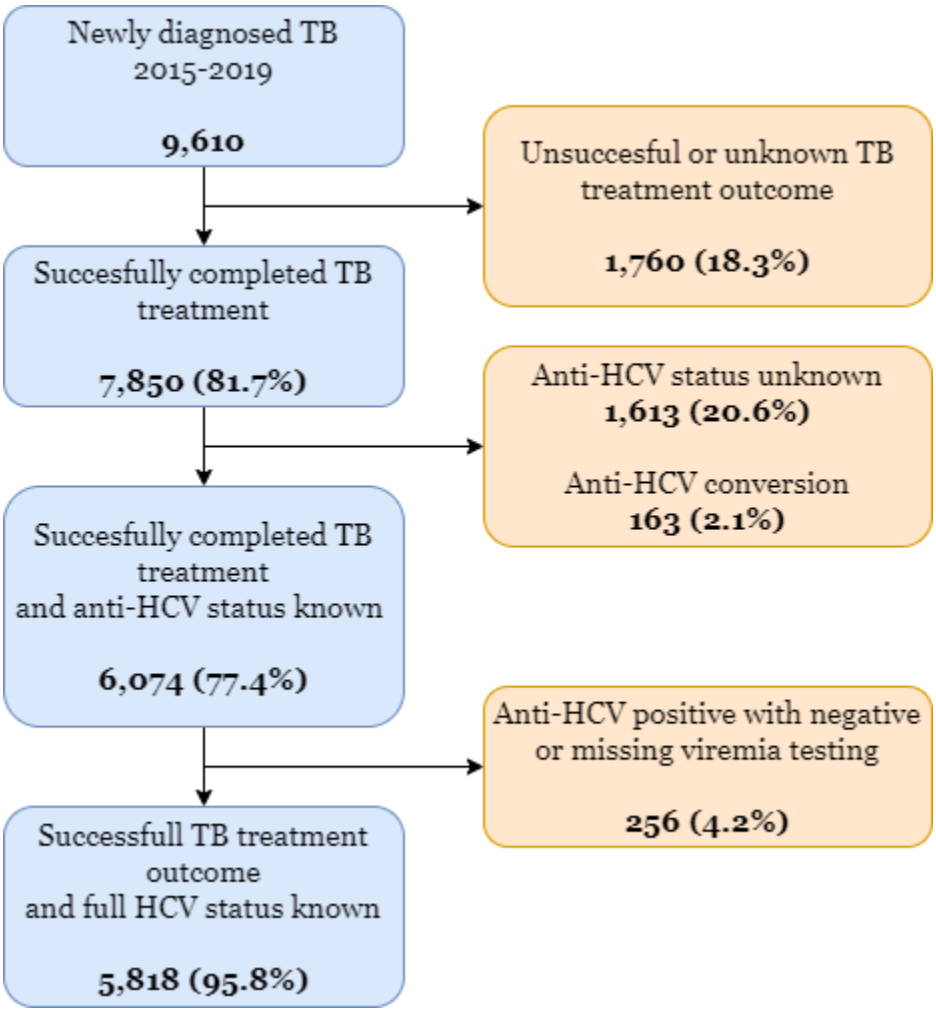
Figure 4.1. Directed acyclic graph (DAG) of factors involved in the relationship of exposure and outcomes of interest.



Note: Green arrows represent hypothesized causal paths. Factors in red were not measured in our study and we were unable to adjust for them.

*SES was not measured directly, and other demographic variables were used as a proxy for SES (Region of residence, employment status, and whether a person was internally displaced from occupied regions of Georgia).

Figure 4.2. Flow chart describing the selection of study population.



Supplemental material for chapter 4

Supplemental Table 4.1. All-cause mortality among patients who successfully completed Second-line TB treatment.

CHARACTERISTICS	Total			All-cause deaths			
	N	%	PY	N	%	Mortality rate per 100,000 PY	Mortality rate ratio (95% CI)
TOTAL COHORT	**436**	**100**	**853**	**18**	**4.1%**	**2111 (1251, 3337)**	
Sex							
Male	282	65%	560	15	5.3%	2679 (1498, 4418)	2.6 (0.8, 9.0)
Female	154	35%	293	3	1.9%	1024 (206, 2991)	1
Region (grouped)							
Tbilisi	224	51%	438	11	4.9%	2511 (1252, 4494)	1
Penitentiary system	8	2%	11	0	0.0%	-	-
Other	204	47%	404	7	3.4%	1733 (694, 3570)	0.7 (0.3, 1.8)
Employment status							
Employed	97	22	189	2	2.1%	1058 (119, 3820)	1

		%					
Unemployed	319	73%	631	14	4.4%	2219 (1212, 3723)	2.1 (0.5, 9.2)
					50.0		47.3 (4.3,
Military	2	0%	2	1	%	50000 (654, 278200)	521.0)
Missing	18	4%	-	1	5.6%	-	-
Diagnosed with TB in penitentiary system							
Yes	8	2%	11	0	0.0%	-	-
No		98					
	428	%	842	18	4.2%	2138 (1266, 3379)	-
History of imprisonment							
Yes	24	6%	48	0	0.0%	0.0	-
No	398	91%	777	17	4.3%	2188 (1274, 3503)	-
Missing	14	3%	-	1	7.1%	-	-
IDP							

	Yes	22	5%	38	2	9.1%	5263 (591, 19000)	2.7 (0.6, 11.8)
			89					
	No	387	%	769	15	3.9%	1951 (1091, 3217	1
	Missing	27	6%	-	1	3.7%	-	-
Year of TB treatment completion								
	2015	0	0%	0	0	0.0%	-	-
	2016	23	5%	88	1	4.3%	1136 (15, 6322)	1
	2017	108	25%	339	8	7.4%	2360 (1016, 4650)	2.1 (0.3, 16.6)
			26					
	2018	112	%	252	2	1.8%	794 (89, 2865)	0.7 (0.1, 7.7)
			26					
	2019	115	%	142	7	6.1%	4930 (1975, 10160)	4.3 (0.5, 35.3)
	2020	78	18%	32	0	0.0%	0.0	-
HIV status								
	Positive	7	2%	20	0	0.0%	0.0	-

Negative	416	95%	809	18	4.3%	2225 (1318, 3517)	-
Missing	13	3%	0	0	0.0%	-	-
Hepatitis C status*							
Never infected	379	87%	729	16	4.2%	2195 (1254, 3564)	1
Infected untreated	45	10%	71	1	2.2%	1408 (18, 7836)	0.6 (0.1, 4.8)
Infected treated	34	8%	52	1	2.9%	1923 (25, 10700)	0.9 (0.1, 6.6)

*Hepatitis C status was treated as time-varying variable and some patients who were treated contributed to the person-time to both treated and untreated group, therefore, total N in this category sums up to more than the actual total number of patients.

Abbreviations: TB, tuberculosis; PY, person-year; CI, confidence interval; HIV, Human Immunodeficiency Virus.

Supplemental Table 4.2. Recurrence of TB among patients who successfully completed DR TB treatment

CHARACTERISTICS	Total			TB recurrence			
	N	%	PY	N	%	Rate per 100,000 PY (95%CI)	Incidence rate ratio (955 CI)
TOTAL COHORT	**435**	**100**	**832**	**10**	**2.3%**	**1202 (611, 2142)**	
Sex							
Male	282	64.8%	546	9	3.2%	1648 (752, 3129)	4.7 (0.6, 37.2)
Female	153	35.2%	286	1	0.7%	350 (5, 1945)	1
Region (grouped)							
Tbilisi	223	51.3%	423	4	1.8%	946 (254, 2421)	1
Penitentiary system	8	1.8%	11	0	0.0%	-	-
Other	204	46.9%	398	6	2.9%	1508 (551, 3281)	1.6 (0.4, 5.6)
Employment status							
Employed	96	22.1%	179	2	2.1%	1117 (126, 4034)	1
Unemployed	319	73.3%	620	8	2.5%	1290 (556, 2542)	1.2 (0.2, 5.4)
Military	2	0.5%	2	0	0.0%	-	-

Missing	18	4.1%		0	0.0%	-	-
Diagnosed with TB in penitentiary system							
Yes	8	1.8%	11	0	0.0%	-	-
No	427	98.2%	822	10	2.3%	1217 (582, 2237)	-
History of imprisonment							
Yes	24	5.5%	45	1	4.2%	2222 (29, 12360)	1.9 (0.2, 14.8)
No	397	91.3%	760	9	2.3%	1184 (540, 2248)	1
Missing	14	3.2%		0	0.0%		
Internally displaced persons							
Yes	22	5.1%	38	0	0.0%	-	-
No	386	88.7%	748	10	2.6%	1337 (640, 2459)	-
Missing	27	6.2%		0	0.0%	-	-
Year of TB treatment completion							

2015	0	0.0%		-	-	-	
2016	23	5.3%	88	0	0.0%	0	
2017	107	24.6%	323	6	5.6%	1858 (678, 4043)	1
2018	112	25.7%	248	3	2.7%	1210 (243, 3534)	0.7 (0.2, 2.6)
2019	115	26.4%	142	1	0.9%	704 (9, 3918)	0.4 (0.05, 3.15)
2020	78	17.9%	32	0	0.0%		
HIV status							
Positive	7	1.6%	17	1	14.3%	5882 (77, 32730)	5.2 (0.7, 40.8)
Negative	415	95.4%	791	9	2.2%	1138 (519, 2160)	1
Missing	13	3.0%					
Hepatitis C status*							
Never infected	378	86.9%	713	7	1.9%	982 (393, 2023)	1
Infected, untreated	45	10.3%	70	2	4.4%	2857 (321, 10320)	2.9 (0.6, 14.0)
Infected treated	34	7.8%	50	1	2.9%	2000 (26, 11130)	2.0 (0.3, 16.6)

*Hepatitis C status was treated as a time-varying variable and some patients who were treated contributed to the person-time to both treated and untreated groups. Therefore, total N in this category sums up to more than the actual total number of patients.

Abbreviations: TB, tuberculosis; PY, person-year; CI, confidence interval; HIV, Human Immunodeficiency Virus.

Chapter 5: Summary and conclusion

Overview of main findings

Tuberculosis and hepatitis C represent major global public health problems. In addition to the burden that these two diseases pose separately, there is a substantial overlap of populations affected with both infections. However, there are critical knowledge gaps about the impact of TB and HCV coinfection and how one infection impacts the other. In this dissertation, we addressed some of these key gaps by looking at the relationship between TB and HCV infection from novel angles. With that purpose, we conducted three large-scale studies in the country of Georgia to address three distinct aims.

In the first study (described in chapter 2 above), we characterized the hepatitis C cascade of care among patients diagnosed with and treated for TB and compared it to a similar cascade of care in the general population without TB. Considering that loss to follow-up is common in Georgia's overall HCV care cascade, we hypothesized that this issue was even more pronounced among patients treated for active TB disease who have HCV coinfection. We found that loss to follow-up from hepatitis C care was a serious problem among patients with TB. Specifically, 20% of adult patients with TB disease and a positive HCV antibody test did not undergo HCV viremia testing to confirm active HCV infection, compared to 14% among patients without TB. Additionally, 43% of those with TB and a positive viremia test (confirming active HCV infection) did not start treatment for hepatitis C in the Georgian elimination program, despite the availability of highly effective oral curative regimens against HCV. Overall, among patients with confirmed active HCV infection, only 28% of patients with TB had a documented cure from HCV, compared to 55% among patients without TB.

The second study (described in chapter 3 above) aimed to explore how hepatitis C affects the risk of TB in a cohort of more than 1.8 million people – the largest cohort to date that has tried to address this question. Additionally, this was the first study of this scale to distinguish between treated and untreated hepatitis C. We found that patients with both treated and untreated hepatitis C have a higher risk of TB than those without HCV infection. However, the effect was much more substantial among those with untreated hepatitis C, suggesting a potential causal role of active HCV infection in enhancing the risk of developing TB disease among those infected with *Mycobacterium tuberculosis*.

The third study (described in chapter 4 above) aimed to assess the effect of HCV on long-term outcomes among patients successfully treated for TB. Specifically, we evaluated all-cause mortality and TB recurrence after TB treatment completion. We found that overall all-cause mortality in patients successfully treated for TB is more than twice higher than in the general population (SMR=2.17). However, the mortality was not different between HCV-positive and negative groups. We also found that untreated HCV infection was associated with an increased risk of TB recurrence among patients with DS TB.

Strengths and limitations

The study-specific strengths and limitations of this dissertation are described in the previous three chapters. This section will review several overarching strengths and limitations relevant to the whole project.

This dissertation project has major strengths that allowed us to produce evidence with major potential clinical and public health implications. First, this project leveraged a unique nationwide population-based data linked to an unprecedented HCV elimination project in Georgia with large sample size and long follow-up time.[115,116] This allowed us to

study rare outcomes, such as incident TB, TB recurrence and death, in an adequately powered analysis. Second, the availability of the national databases, all of which uses national ID number, allowed us to link different sources of data to each other and answer research questions that would be impossible to explore using any single data source by itself. Third, this project benefitted from the support and expertise of a multidisciplinary team of clinicians, statisticians, and epidemiologists from multiple institutions in the US and Georgia. This collaborative team allowed us to conduct methodologically sound research studies that have implications for multiple public health programs in the country of Georgia.

One limitation of the dissertation studies was the lack of a measure for socioeconomic status (SES), which could be an important confounder of the association between HCV infection and TB. TB-related data contained a variable about employment status, but a similar variable was unavailable in the hepatitis C screening registry. One of the potential sources for the SES is the database of the socially vulnerable persons under the poverty limit who receive financial aid from the state. We tried to obtain this database from the Georgian Ministry of Health. However, due to local laws regarding the protection of personal information, we were unable to find a legal mechanism to receive the data containing national ID numbers that would allow us to link individual data to our datasets. This limitation hampered our ability to adjust for the low SES as a potential confounder in several of our analyses. We adjusted our models for factors closely correlated with the SES, such as the municipality of residence and employment status, to alleviate this issue. Therefore, it can be assumed that our analyses generated robust and reliable findings despite the lack of direct measurement of SES.

Another potential confounder that needs to be considered in the relationship between

HCV infection and TB is injection drug use (IDU), a shared risk factor for both infections. For confidentiality reasons, data on injection drug use are not recorded for all patients using the national ID number in the hepatitis C screening registry. Additionally, the question about past or current injection drug use is not asked in the hepatitis C screening process. For that reason, we were not able to directly adjust for the injection drug use in our analyses. This might have the biggest impact on aim 2 of this dissertation, where we assessed the association between HCV infection and the risk of TB. We addressed this issue by using quantitative bias analysis methods for unmeasured confounding.

Implications

This dissertation project generated evidence that has potential implications for clinical management and overall control of both tuberculosis and hepatitis C. The HCV care cascade analysis provided estimates about what proportion of patients with active TB that test positive on HCV antibody testing undergo confirmatory testing and, if HCV infection is confirmed, what proportion started treatment for HCV infection after they became eligible. Our findings suggest higher loss to follow-up among patients with TB (compared to those without TB disease) and support the idea that a more integrated approach is needed for the management of patients with TB and HCV coinfection. For example, national TB and hepatitis C programs should consider treating uncomplicated HCV patients in the same facilities where they received treatment for TB, without interruption after TB treatment completion. Because of complex drug-drug interactions, simultaneous treatment of TB and HCV is often not feasible, but sequential treatment is. Findings from this analysis were presented at the Georgian HCV elimination program scientific committee and at the technical advisory group (TAG) meeting. The need for more

integrated testing and treatment of patients with TB and hepatitis C was reflected in TAG recommendations and the new strategy for eliminating viral hepatitis in Georgia for 2021-2025.

Our second study found a substantially higher incidence of TB among patients with hepatitis C, highlighting that interventions targeted at prevention or early detection of TB in patients with hepatitis C will be beneficial. Our findings provide a rationale to introduce routine screening for LTBI and active TB among persons with HCV infection. They also provide evidence in support for LTBI treatment in this population. According to the Georgian 2019 guidelines for TB management, LTBI treatment is recommended for patients with HIV, and some high-risk HIV-negative individuals, such as prisoners and PWID, but not for those with chronic HCV infection. Additionally, international guidelines do not currently recommend LTBI testing and treatment among patients with chronic hepatitis C. However, there is no evidence supporting the contraindication of LTBI treatment during chronic hepatitis C. This caution is caused by concerns about the hepatotoxic activity of some of the medications used in LTBI treatment. Furthermore, there are newer treatment regimens available for LTBI treatment that could, in theory, be safely used for patients with hepatitis C. A future study assessing the LTBI treatment in patients with HCV could generate valuable evidence and should be considered by agencies and donors.

Findings in our third study highlight the importance of post-treatment care among patients with TB. Reducing TB mortality is one of the priorities proposed by the WHO's End TB Strategy. We found that high mortality is an issue even after successfully treating patients with TB (irrespective of hepatitis C status). Further, the association of hepatitis C infection and TB recurrence suggests that the existing infrastructure of hepatitis C

programs in Georgia or elsewhere could be used for post-treatment evaluation of patients who completed TB treatment and initiated hepatitis C treatment.

Future directions

This dissertation project provides a basis for a variety of future research projects and analyses. Some of these analyses can be carried out with existing data already compiled for this dissertation, while other projects will require additional data sources to be obtained and linked to the current databases.

1. **LTBI testing and treatment among patients with HCV**: In the current project, we did not have any LTBI data available on patients with HCV. If we obtain funding for a prospective study, we would be able to test patients enrolled in the HCV elimination program for LTBI and, in the absence of contraindications, offer them LTBI treatment. This project will generate valuable information about the feasibility and effectiveness of treating patients with hepatitis C for LTBI.
2. **Impact of HCV infection on TB treatment outcomes:** As one of the next steps, we plan to explore whether or not HCV infection affects the TB treatment success and if patients with HCV coinfection are required to interrupt the TB treatment more commonly. All data for this analysis are already obtained and available in the datasets created for this dissertation.
3. **Evaluating the morbidity and hospitalization rate due to the coinfection of TB and HCV infection:** Using the national database of hospitalized patients, we will explore other health outcomes in patients with TB/HCV coinfection. More specifically, we will evaluate the effect of coinfection on the morbidity and hospitalization rate due to lung- and liver-related complications.

4. **Cause-specific mortality among patients with TB/HCV coinfection:** As a follow-up to aim 3 of this dissertation, we will attempt to obtain the causes of death from nationwide sources. Based on the personal communications with representatives of NCDC, substantial steps have been made to improve the quality of reporting causes of death to the death registry in recent years. Updated mortality data will allow us to evaluate cause-specific mortality instead of all-cause mortality among patients with coinfection.

In conclusion, this project can be considered a successful first step in addressing the gaps of knowledge about the epidemiology and impact of overlap between hepatitis C and TB, and it also provides multiple future opportunities to explore the other angles of this overlap.

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