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# Association of Treated and Untreated Chronic Hepatitis C With the Incidence of Active Tuberculosis Disease: A Population-Based Cohort Study

**Davit Baliashvili**[1], **Henry M. Blumberg**[1,2], **David Benkeser**[3], **Russell R. Kempker**[2], **Shaun Shadaker**[4], **Francisco Averhoff**[5], **Lia Gvinjilia**[6], **Natalia Adamashvili**[7], **Matthew Magee**[8], **George Kamkamidze**[9], **Mamuka Zakalashvili**[10], **Tengiz Tsertsvadze**[11], **Lali Sharvadze**[12,13], **Mamuka Chincharauli**[14], **Nestan Tukvadze**[14], **Neel R. Gandhi**[1,2,8]

[1]Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, Georgia, USA;

[2]Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA;

[3]Department of Biostatistics and Bioinformatics, Emory University Rollins School of Public Health, Atlanta, Georgia, USA;

[4]Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia, USA;

[5]Department of Family and Preventive Medicine, Emory University School of Medicine, Atlanta, Georgia, USA;

[6]Eastern Europe and Central Asia Regional Office, Centers for Disease Control and Prevention, Tbilisi, Georgia;

[7]National Center for Disease Control and Public Health, Tbilisi, Georgia;

[8]Department of Global Health, Emory University Rollins School of Public Health, Atlanta, Georgia, USA;

[9]Health Research Union and Clinic NeoLab, Tbilisi, Georgia;

[10]Clinic “Mrcheveli”, Tbilisi, Georgia;

[11]Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia;

[12]Clinic “Hepa”, Tbilisi, Georgia;

[13]The University of Georgia, Tbilisi, Georgia;

[14]National Center for Tuberculosis and Lung Diseases, Tbilisi, Georgia

Correspondence: D. Baliashvili, 99 Kakheti Hwy, Tbilisi, Georgia, 0198. The Task Force for Global Health contractor for CDC country office in Georgia (davit.baliashvili@emory.edu; or dato.baliashvili@gmail.com).

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

***Disclaimer.*** The findings and conclusions in this report are those of the authors and not necessarily the official position of the US Centers for Disease Control and Prevention.

## Abstract

**Background.—**Hepatitis C virus (HCV) infection causes dysregulation and suppression of immune pathways involved in the control of tuberculosis (TB) infection. However, data on the role of chronic hepatitis C as a risk factor for active TB are lacking. We sought to evaluate the association between HCV infection and the development of active TB.

**Methods.—**We conducted a cohort study in Georgia among adults tested for HCV antibodies (January 2015–September 2020) and followed longitudinally for the development of newly diagnosed active TB. Data were obtained from the Georgian national programs of hepatitis C and TB. The exposures of interest were untreated and treated HCV infection. A Cox proportional hazards model was used to calculate adjusted hazard ratios (aHRs).

**Results.—**A total of 1 828 808 adults were included (median follow-up time: 26 months; IQR: 13–39 months). Active TB was diagnosed in 3163 (0.17%) individuals after a median of 6 months follow-up (IQR: 1–18 months). The incidence rate per 100 000 person-years was 296 among persons with untreated HCV infection, 109 among those with treated HCV infection, and 65 among HCV-negative persons. 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 infections were associated with a higher hazard of active TB, compared with HCV-negative persons.

**Conclusions.—**Adults with HCV infection, particularly untreated individuals, were at higher risk of developing active TB disease. Screening for latent TB infection and active TB disease should be part of clinical evaluation of people with HCV infection, especially in high-TB-burden areas.

### Keywords

tuberculosis; hepatitis C; cohort

Globally, tuberculosis (TB) has been the leading infectious disease cause of death before the coronavirus disease 2019 (COVID-19) pandemic. In 2020, an estimated 10 million people developed active TB disease, and there were 1.5 million deaths due to TB [1]. Additionally, an estimated 1.7 billion people worldwide are infected with *Mycobacterium tuberculosis* (*Mtb*) and are at risk of developing active TB disease during their lifetime [2]. Hepatitis C virus (HCV) infection is another major global public health problem. According to the World Health Organization (WHO), 58 million people were living with chronic hepatitis C in 2019, 1.5 million new cases occur each year, and 290 000 people died due to hepatitis C in 2019 [3]. The hepatitis C epidemic affects all parts of the world, with the highest prevalence in the WHO's eastern Mediterranean and European regions [4]. There is a substantial overlap in population subgroups affected by HCV and TB, with injection drug use a common risk factor for both infections. However, the role of chronic HCV infection in developing active TB disease is not established.

Risk factors for progression from latent TB infection (LTBI) to active TB disease include immunocompromising conditions such as human immunodeficiency virus (HIV) infection, diabetes, smoking, and organ transplantation [5]. HCV infection is associated with impairment of macrophage activation and T-cell responses—key components for successful

host response to *Mtb* [6–8]. However, the role of HCV infection as a risk factor for active TB disease has not been adequately studied at the population level. Several studies suggest that those with chronic HCV infection are at higher risk of active TB disease [9–11], but compelling evidence is lacking due to a small number of longitudinal studies assessing this association. Due to this knowledge gap, screening for latent infection or active TB disease is not typically recommended among patients diagnosed with chronic hepatitis C [12, 13].

This study aimed to assess how untreated and treated chronic HCV infection status impacts the incidence of active TB disease. Our a priori hypothesis was that the incidence of active TB is highest among those with untreated chronic HCV infection, followed by those who were treated for chronic HCV infection, and lowest among those never infected with HCV. A large nationwide hepatitis C elimination program in the country of Georgia provides a unique opportunity to estimate population-level active TB incidence rates among individuals with hepatitis C infection. Demonstrating an association between HCV infection and increased risk of active TB disease would provide initial evidence for routine screening for 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 [14].

## METHODS

### Setting

The eastern European country of Georgia (population 3.7 million) is a WHO high-priority country for TB prevention and care in the European region [15] (TB incidence: 70 cases per 100 000 in 2020) [1]. All diagnostic and treatment services for active TB disease are provided free of charge within the Georgian National TB Program. Tuberculosis surveillance data are collected in a centralized National TB Program database at the National Center for Tuberculosis and Lung Diseases [16]. During the study period, the LTBI testing and treatment were only offered to high-risk groups, such as children younger than 5 years and people living with HIV. Persons with HCV infection or other population not representing high-risk groups are usually not offered LTBI treatment [17].

Chronic HCV infection is also highly prevalent in Georgia, affecting 5.4% of the general adult population (~150 000 individuals) in 2015, making it among the 10 countries with the highest prevalence worldwide [18, 19]. 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 [20]. The program provides free hepatitis C testing and treatment with direct-acting antivirals (DAAs) for all citizens [21, 22]. The country integrated screening through HCV antibody testing into multiple settings, such as blood safety, antenatal surveillance, harm reduction, inpatient settings, prisons, and national HIV and TB programs [21, 23–26]. All hepatitis C screening and clinical data are entered into nationwide databases.

## Study Design and Population

We conducted a cohort study among adult residents of Georgia tested for HCV antibodies. The study period was 1 January 2015–30 September 2020. Exclusion criteria were as follows: (1) missing national ID number in HCV testing data, (2) missing or conflicting dates necessary for incidence calculations (dates of HCV antibody testing, death, or hepatitis C treatment completion), and (3) known diagnosis of active TB disease before or at the time of the first HCV antibody testing. People who had a conversion of HCV antibody testing results (n = 17 323) or those with positive HCV antibody results with negative or missing viremia testing (n = 33 128) were retained in descriptive analysis and incidence calculations but excluded from the multivariable models (Figure 1).

## Data Sources

Hepatitis C testing and treatment information was obtained from 2 nationwide electronic databases: the National HCV Screening Registry and Hepatitis C Elimination Program database (ElimC) [23]. The outcome (diagnosis of active TB disease) was ascertained from the national TB surveillance database. Mortality data were extracted from the national death registry; date of death was obtained, but causes of death were not available. The linking variable was the national ID number—a unique identifier used in all databases.

## Variables and Definitions

The baseline date was defined as the date of the first known HCV antibody 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 as 1 January 2015. Chronic HCV infection was defined as a positive HCV antibody test followed by a positive viremia test (HCV RNA or core antigen). We assumed that the proportion of viremia-positive cases that spontaneously clear the infection is negligible since the majority of individuals in our sample were likely chronically infected, whereas spontaneous clearance typically occurs within months of initial infection [27].

Persons with chronic HCV infection were further defined as treated for hepatitis C if they finished a treatment course within the hepatitis C elimination program, regardless of whether their sustained virologic response (SVR) testing was performed; all other individuals were categorized as untreated HCV. If a person had more than 1 episode of hepatitis C treatment (ie, reinfection or re-treatment after treatment failure), the treatment completion determination was based on the latest hepatitis C treatment.

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

## Statistical Analysis

Unadjusted incidence rates of active TB disease were calculated in 5 groups with different HCV infection status: (1) no evidence of HCV infection (negative result on HCV antibody test); (2) treated HCV infection, irrespective of SVR status; (3) untreated HCV infection; (4) unknown infection status (positive HCV antibodies without viremia testing); and (5)

spontaneously cleared infection (positive HCV antibodies and negative viremia result, without documented treatment). Person-time was calculated as the number of days from the baseline to (1) first active TB diagnosis, (2) death, or (3) end of the study period (30 September 2020). Crude incidence rate ratios and 95% confidence intervals (CIs) were calculated for each of the 5 HCV status groups, with the no-evidence-of-HCV-infection group serving as the reference.

Multivariable analysis was performed using Cox proportional hazards regression. The model used age as the time scale and was stratified by birth cohort (5-year intervals) to adjust for the birth cohort effects. The primary exposure of interest was the status of HCV infection with 3 categories: (1) untreated HCV infection, (2) treated HCV infection, and (3) absence of HCV infection (reference category). The primary outcome of interest was newly diagnosed active TB disease. Hepatitis C treatment was included 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 included in the model (sex, age, imprisonment, and municipality as a proxy for socioeconomic status) based on directed acyclic graph theory (Supplementary Figure 1) [28].

Because a substantial proportion of persons had positive HCV antibodies but did not undergo viremia testing (n = 21 277; 18% of all HCV antibody-positive individuals), we conducted inverse probability of selection weighting to address the potential for selection bias. Study participants with viremia testing were reweighted so that they represented themselves, plus some of the persons in the source population who were eligible but not included in the final analysis (ie, tested for HCV antibodies but not for viremia). The weights were derived based on age, sex, municipality, and imprisonment status; and multivariable analyses with Cox models were repeated using these weights.

## Sensitivity Analysis

We conducted sensitivity analyses to explore how the findings might have changed using different assumptions and definitions. We ran 3 additional multivariable models, each with several modifications. The first sensitivity analysis model repeated the multivariable analysis using the date of the first hepatitis C treatment initiation as a switching point between treated and untreated states among patients who received hepatitis C treatment. The second model excluded patients treated for hepatitis C infection who were tested for SVR and found not to have achieved cure. The third model excluded patients treated for hepatitis C who either did not achieve SVR or did not get tested for SVR. Additionally, we conducted a quantitative bias analysis for unmeasured confounding due to injection drug use (IDU) and calculated the E-value for other unmeasured confounders [29–31] (Supplementary Material).

## Ethics

The study was approved by the institutional review boards (IRBs) at the National Center for Disease Control and Public Health of Georgia, the National Center for Tuberculosis and Lung Disease of Georgia, and Emory University.

# RESULTS

## Description of the Study Population

The initial study population consisted of 1 849 678 adults tested for HCV antibodies during the study period—65% of the total adult population of Georgia. We excluded 12 156 (0.7%) persons with previous or current active TB at the time of HCV antibody testing and 8714 (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 (inter-quartile range [IQR]: 31–62) years. Most people were tested for 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 (IQR: 13–39 months), with a total of 4 212 327 person-years (PYs) of follow-up. People who had a conversion of HCV antibody results (n = 17 323) or those with positive HCV antibody results with negative or missing viremia testing (n = 33 128) were retained in descriptive analysis but excluded from the primary multivariable models (Figure 1), which focused on the 1 778 357 individuals within 3 main comparison groups. At baseline, there was a higher proportion of males in both untreated and treated hepatitis groups (1.6% and 5.3%, respectively) compared with females (0.4% and 1.2%, respectively). The proportion of people never infected with HCV increased by year from 81% in 2015 to 98% in 2020 (Supplementary Table 1).

## Active Tuberculosis by HCV Infection Status

Among our analytic cohort of 1 828 808 individuals, there were 3163 (0.17%) individuals newly diagnosed with active TB after a median of 6 months (IQR: 1–18 months); this equated to an active TB incidence rate of 75.1 per 100 000 PYs (Table 1). The un-adjusted incidence of newly diagnosed active TB among people with untreated HCV infection (296 cases per 100 000 PYs; 95% CI: 264–331 cases) was more than 4 times higher than the incidence in those never infected with HCV (65 cases per 100 000 PYs; 95% CI: 62–68 cases) (Table 2). The incidence of active TB in people with treated HCV was 1.7-times higher (109.1 cases per 100 000 PYs: 95% CI: 93.1–127.1 cases) than in those without HCV, suggesting that chronic and ongoing HCV infection plays a key role in the increased risk of active TB disease diagnosis. In fact, if we restrict our analysis to patients treated for HCV who had documented HCV cure, the incidence was further reduced to 1.5-times greater (99.1 cases per 100 000 PYs; 95% CI: 81.9–118.9 cases) than those who never had HCV infection. Similarly, individuals who had a positive HCV antibody test but a negative viremia test in the absence of documented treatment—those who likely spontaneously cleared the HCV infection—had an active TB incidence of 2.2-times greater (141 cases per 100 000 PYs; incidence rate ratio: 2.1) (Table 2).

In the multivariable analysis comparing the 3 main groups of people with known HCV status (untreated HCV infection, treated HCV, and never infected), those with untreated HCV infection remained at the greatest rate for active TB disease (adjusted hazard ratio [aHR] = 2.9; 95% CI: 2.4–3.4) compared with persons never infected with HCV (Table 3). Individuals with HCV who were treated also had an increased rate of active TB (aHR = 1.7; 95% CI: 1.4–2.0), although it was less than those with untreated HCV.

The precise aHRs of our findings changed only slightly in the sensitivity analysis models (Table 3). The aHRs for the untreated HCV group compared with the no-HCV group 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 (ie, sensitivity analysis 3: aHR = 1.5; 95% CI: 1.2–1.9) (Table 3). After quantitative bias-adjustment for IDU, we observed a shift of estimated measures of association towards the null association for both treated and untreated groups. Still, both groups remained associated with the active TB disease (Supplementary Table 2).

## DISCUSSION

In this study, we assessed the impact of chronic HCV infection on the risk of developing active TB disease. We linked population-level information that measured HCV infection and active TB disease from the country of Georgia, where an unprecedented nationwide HCV elimination program is taking place. We evaluated a cohort of more than 1.8 million people, the largest cohort study to date evaluating the relationship between HCV and active TB disease. We found that the incidence of active TB was higher in all groups with hepatitis C exposure and infection. The highest incidence occurred among people with untreated chronic hepatitis C infection, who had nearly 3 times the increased risk of developing active TB; this association remained in all sensitivity analyses and after bias-adjusting for IDU as an unmeasured confounder. The incidence of active TB diminished substantially with treatment of hepatitis C and was attenuated further in sensitivity analyses restricted to those with documented HCV cure and bias adjustment for IDU. These findings suggest that the increased risk of active TB disease is associated with active HCV infection itself and not by its sequelae or other unmeasured factors.

Our findings suggesting an association between chronic HCV infection and development of active TB are supported by prior studies and have biological plausibility. Our results are consistent with a 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 [9]. Although our study was not designed to demonstrate a causal relationship between HCV and active TB disease, such a causal association is biologically plausible. HCV can impact a host’s immune system, increasing the risk of active TB disease immediately after initial exposure to *Mtb*, as well as by increasing the risk of reactivation from LTBI to active TB disease.

A recent study showed that patients with both active TB and hepatitis C had lower expression of markers of CD4 T-cell activation compared with patients with only TB or hepatitis C [7]. There are several hypothesized immunologic mechanisms by which HCV infection might increase the risk of TB: (1) chronic HCV infection reduces the production and concentration of cytokines (eg, 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 [8]; (2) HCV infection increases the level of inhibitory cytokines,

such as interleukin (IL)-10, which inhibit cytokines required for an effective response to *Mtb* including IL-12, IFN-γ, and TNF-α [32]; (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* [33, 34]); and (4) viral persistence during chronic hepatitis C can cause the development of functionally inferior T cells—a condition referred to as T-cell exhaustion [35, 36]. 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* [6].

A noteworthy finding of our study is that the risk of TB disease is greatest among individuals with chronic HCV who have not been treated for HCV; the TB risk diminishes among those treated for HCV, suggesting that ongoing HCV infection plays a role in the TB risk. Immunologic studies in patients after DAA treatment show conflicting results. Some studies suggest partial improvement in immune functions after SVR, while others did not demonstrate any reconstitution in CD8 T-cell function and IFN-γ production [37]. Our findings support the hypothesis that there is improvement in immune functions responsible for *Mtb* control among patients treated for HCV, suggesting the indirect benefit of HCV treatment on the risk of TB disease.

Our study suggests that people with hepatitis C should be considered for inclusion as a priority group for TB prevention and care efforts. This would have at least 2 important implications for TB programs. First, patients with hepatitis C should be considered for preventive measures, such as LTBI treatment. LTBI testing or treatment is currently not prioritized for patients with HCV infection globally due to fears of hepatotoxic activity of medications used for LTBI treatment. However, there are newer LTBI treatment regimens with potentially lower hepatotoxic effect. These data may catalyze a change in practice. A logical next step could be a small-scale feasibility study assessing the safety and tolerability of LTBI treatment among patients with HCV infection. Second, the integration of active TB screening measures for patients diagnosed with hepatitis C could increase TB case detection. Diagnostic and treatment delays are impediments to TB prevention and care globally [38, 39]. Identifying an additional risk group that could benefit from the routine screening will help in the timely diagnosis and prevention of active TB and would thus contribute to decreasing the overall TB incidence.

Our study had several limitations. First, our data did not include some variables that can confound the associations between HCV and active TB, such as IDU, socioeconomic status, HIV infection, alcohol use, and history of incarceration. We adjusted for municipality as a proxy variable for socioeconomic status and used quantitative bias-analysis methods to adjust for IDU as a confounder. Inability to adjust for HIV infection likely did not affect our findings meaningfully because HIV prevalence is low in Georgia, and it is not a substantial contributing factor for TB cases overall or among people with HIV/HCV coinfection [1, 40, 41]. Additionally, our sensitivity analysis for unmeasured confounders suggests that any unmeasured confounder will need to be associated with more than 5-times higher risk of both exposure and outcome to fully explain our observed association between untreated

hepatitis C and active TB (Supplementary Material). Second, if people diagnosed with HCV infection are more likely to undergo TB diagnostic assessment, it is possible that the association of untreated and treated HCV infection with active TB disease is overestimated. Last, our study did not capture individuals who have not been screened for hepatitis C. Nonetheless, our study population captures 65% of the adult population of the country, and the TB incidence found in the study (75.1 per 100 000 PYs) is comparable to the TB incidence among the general Georgian population (70 per 100 000 PYs in 2020).

In conclusion, in this large population-based cohort study involving 1.8 million adults, we found a strong association between untreated hepatitis C and the diagnosis of active TB. Our findings highlight the importance of timely and accessible hepatitis C treatment, which might provide collateral benefit by decreasing the risk of TB, in addition to being highly effective against the HCV infection itself. Screening for active TB disease and treatment for LTBI among people with HCV infection might reduce TB incidence and improve early detection of active TB disease, which are priorities of the WHO's End TB strategies.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### Potential conflicts of interest.

F. A. reports stock or stock options in Abbott Diagnostics and other financial or nonfinancial interests through Abbott Diagnostics and the Centers for Disease Control and Prevention. H. M. B. reports grants or contracts from the NIH. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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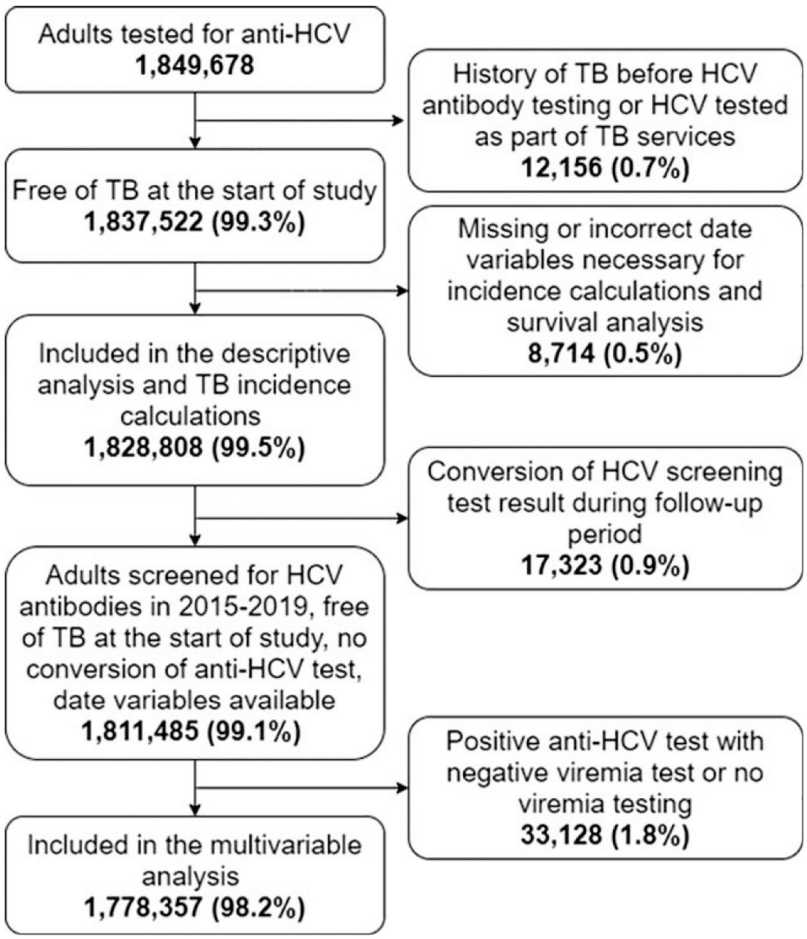


**Figure 1.**

Flow chart of study population: persons tested for HCV antibodies, 1 January 2015–30 September 2020. Abbreviations: anti-HCV, hepatitis C virus antibody; HCV, hepatitis C virus; TB, tuberculosis.

**Table 1.**

Descriptive Statistics of Study Population and Incidence of Newly Diagnosed Active Tuberculosis (TB): Adults Tested for Hepatitis C Virus Antibodies in Georgia Between 1 January 2015 and 30 September 2020, Without Prior TB Diagnosis

| | Total | | New Active TB | | | |
|---|---|---|---|---|---|---|
| **Demographic Characteristics** | **n** | **Column (%)** | **n** | **Row (%)** | **PYs** | **TB IR per 100 000 PYs** |
| Total cohort | 1 828 808 | 100 | 3163 | 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 HCV antibody 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[a] | 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 |
| People who are incarcerated | 8770 | 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 |

| Demographic Characteristics | Total | | New Active TB | | PYs | TB IR per 100 000 PYs |
|---|---|---|---|---|---|---|
| | n | Column (%) | n | Row (%) | | |
| Missing | 33 051 | 2 | 95 | 0.29 | 94 960 | 100.0 |
| At least 1 positive HCV antibody 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 |

Abbreviations: anti-HCV, antibodies against hepatitis C virus; HCV, hepatitis C virus; IR, incidence rate; NCDC, National Center for Disease Control; PY, person-year; TB, tuberculosis.

[a]The high incidence rate of TB in 2020 is likely caused by the pandemic-related lockdowns in the first half of the year (March–May). Anti-HCV testing was lower in early months of 2020 and increased in summer, which caused the number of people included in the analysis for 2020 to increase but their contribution to person-time was very short and resulted in a small denominator, increasing the rate.

**Table 2.**

Unadjusted Incidence Rates of Newly Diagnosed Active Tuberculosis by Hepatitis C Virus Infection Status (per 100 000 Person-Years, N = 1 828 808)

| Group | n | TB Cases | PYs | IR (95% CI) | IRR 95% CI |
|---|---|---|---|---|---|
| Never infected with HCV | 1 708 017 | 2499 | 3 847 497 | 65.0 (62.4, 67.6) | 1 |
| Untreated HCV infection | 70 341[a] | 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) |
| Conversion of HCV antibody test result[b] | 17 323 | 133 | 56 449 | 235.6 (197.3, 279.2) | 3.6 (3.0, 4.3) |
| HCV antibody positive/viremia negative | 15 921 | 84 | 59 607 | 140.9 (112.4, 174.5) | 2.2 (1.7, 2.7) |
| HCV antibody positive/viremia missing | 21 277 | 110 | 50 998 | 215.7 (177.3, 260.0) | 3.3 (2.7, 4.0) |

Individual groups are not mutually exclusive. Some individuals from the group of anti-HCV result conversion are also included in the anti-HCV positive/viremia negative and anti-HCV positive/viremia missing groups.

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

[a]Includes both treated and untreated individuals because those treated contributed person-time to the untreated group until the date of the last hepatitis C treatment completion.

[b]Change in HCV antibody test result from negative to positive during the study period, indicating a recent infection.

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**Table 3.**

Multivariable Models Assessing the Association of Untreated and Treated Hepatitis C With Active Tuberculosis

| | aHR (95% CI)[a] | | | | |
|---|---|---|---|---|---|
| **HCV Category** | **Main Model Without IPW** | **Main Model With IPW** | **Sensitivity Analysis 1** | **Sensitivity Analysis 2** | **Sensitivity Analysis 3** |
| Untreated HCV infection | 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) |
| Treated HCV infection | 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) |
| Never infected with HCV | 1 | 1 | 1 | 1 | 1 |

Adults tested for HCV antibodies between 1 January 2015 and 30 September 2020 (N = 1 778 383). Definitions for untreated and treated HCV infection differed between the main model and sensitivity analysis models. Exact definitions used for each model are provided in the “Methods” section.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HCV, hepatitis C virus; IPW, inverse-probability weighting.

[a]Adjusted for sex, municipality, and imprisonment. Models used age as the time scale and controlled the birth cohort using stratification.