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Characteristics and TB treatment outcomes in TB patients with viral hepatitis, New York City, 2000–2010

G. BUSHNELL[1,2], N. L. STENNIS[1], A. M. DROBNIK[1], D. C. PROOPS[1], S. D. AHUJA[1], K. BORNSCHLEGEL[1] AND J. FULD[1]*

[1] *New York City Department of Health and Mental Hygiene, Division of Disease Control, Long Island City, NY, USA*
[2] *University of North Carolina Gillings School of Public Health, Department of Epidemiology, Chapel Hill, NC, USA*

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SUMMARY

Literature surrounding the burden of and factors associated with hepatitis B virus (HBV) and hepatitis C virus (HCV) infection in persons with tuberculosis (TB) disease remains limited and focused on populations outside the USA. Cross-matched New York City (NYC) TB and viral hepatitis surveillance data were used to estimate the proportion of NYC adults diagnosed with TB from 2000 to 2010 with a report of viral hepatitis infection and to describe the impact of viral hepatitis infection on TB treatment completion and death. For 9512 TB patients, HCV infection was reported in 4·2% and HBV infection in 3·7%; <1% of TB patients had both HCV and HBV infection. The proportion of TB patients with HCV infection to die before TB treatment completion was larger than in TB patients without a viral hepatitis report (21% *vs.* 9%); this association remained when stratified by HIV status. There was no significant difference in death before treatment completion for TB patients with HBV infection compared to TB patients without a viral hepatitis report when stratified by HIV status. These findings reinforce the importance of hepatitis testing and providing additional support to TB patients with viral hepatitis infection.

Key words: Hepatitis C, hepatitis B, surveillance, infectious disease epidemiology, tuberculosis (TB).

INTRODUCTION

In 2012, an estimated 8·6 million people worldwide developed tuberculosis (TB), resulting in an incidence rate of 122 cases/100 000 people [1]. In the USA, TB control efforts reduced the rate of TB in 2012 to 3·2 cases/100 000; however, if decline continues at the recent pace, TB elimination will not be achievable in this century [2]. To continue to reduce TB incidence and mortality, TB programmes have sought to identify groups at increased risk for TB infection as well as conditions that increase the likelihood of progression to TB disease. These efforts have revealed the importance of other diseases in the course of TB disease. For example, globally HIV and diabetes are recognized as highly prevalent conditions that increase the risk of developing active TB disease and having poor TB treatment outcomes, including death [3–7].

Less is known about the prevalence of viral hepatitis infection in persons with TB and its impact on TB treatment outcomes. Viral hepatitis infection has important

* Author for correspondence: J. Fuld, PhD, Director, PCSI, Division of Disease Control, New York City Department of Health and Mental Hygiene, 42–09 28th Street, 5th Floor, Queens, NY 11101, USA.
(Email: jfuld@health.nyc.gov)

clinical implications for persons undergoing treatment for TB, as drug-induced hepatotoxicity and hepatic dysfunction are more common in TB cases co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) than in patients without viral hepatitis. As a result, these patients may be less likely to successfully complete TB treatment [8–10], although one study found that TB patients with HCV infection who developed drug-induced hepatotoxicity were able to resume and successfully complete TB treatment after HCV treatment with alpha-interferon [11].

Most estimates of the prevalence of viral hepatitis in persons with TB are based on populations outside the USA. The sole published study conducted in a US-based population, using cross-matched surveillance data from Seattle, King County, Washington, found that 3·6% of TB patients had HCV infection [12]. In other parts of the world, prevalence estimates of HCV infection in TB patients range from 2% to 31% [13–19]. HBV infection prevalence in TB patients has not previously been reported in the USA, and estimates from other countries range from 4% to 26% [8, 13, 14, 18, 20, 21].

New York City (NYC) had the highest TB burden of any city in the USA in 2012 and TB incidence in NYC was more than twice the national rate (8·0 *vs.* 3·2 cases/100 000) [2, 22]. Prevalence estimates of HBV infection and HCV infection are also higher in NYC than the USA as a whole [23–26]. The elevated burden of these diseases in NYC suggests a need for novel approaches. Improved understanding of the relationship between TB disease and viral hepatitis infection in NYC may reveal opportunities for coordinated outreach and care and inform efforts to improve individual TB treatment outcomes while further reducing TB incidence and mortality in NYC. In this descriptive analysis, we estimate the proportion of persons with TB in NYC with a report of HCV or HBV infection; describe the demographic, social, and clinical characteristics associated with HCV and HBV infection in TB patients; and assess the impact of HBV and HCV co-infection on TB treatment outcomes, specifically TB treatment completion and death.

METHODS

Data source

In 2010, the NYC Department of Health and Mental Hygiene (DOHMH) implemented the Centers for Disease Control and Prevention's Program Collaboration and Service Integration (PCSI) initiative to increase data sharing between infectious disease programmes. Cross-matched data were used to identify TB cases who matched with the HBV, HCV, or HIV surveillance registries or the death certificate registry [27]. Patient characteristics were drawn from the TB registry; these data are enriched through TB case management activities, including chart reviews and patient interviews. HBV infection was defined as a positive result for HBV surface antigen, e antigen, or nucleic acid test. HCV infection was defined as a positive result for an enzyme-linked immunosorbent assay antibody test, recombinant immunoblot assay, or nucleic acid test. Only reporting of positive test results were mandated by the NYC Health Code during the analytical period. The viral hepatitis surveillance registry does not contain information on the total number of persons tested for viral hepatitis infection. For this analysis, persons with no report of HCV or HBV infection were treated as uninfected with viral hepatitis.

Analytical population

The population for this analysis included all NYC residents diagnosed with TB between 1 January 2000 and 31 December 2010. End of TB care was defined as the date TB therapy stopped, or if this was missing, the date case management activities ended. TB patients with end of care after 31 December 2010 were excluded. Persons aged <18 years at TB diagnosis were excluded to improve comparability of the reference groups, as only two reports of viral hepatitis were found for this age group. The dataset was also limited to a person's first TB diagnosis. Individuals with multidrug-resistant (MDR) TB, defined as resistance to at least isoniazid and rifampin, were excluded as resistance to first-line TB drugs increases the likelihood of poor TB outcome [28]. Based on the match results, a person with TB was defined as having HCV or HBV infection if the first surveillance report of HCV or HBV infection occurred before the end of TB care. Persons with TB could have reports of both HCV and HBV infection; due to the small number of persons with both HCV and HBV infection, this subset was not analysed separately.

Variables

Patient characteristics measured included sex, age at TB diagnosis, birth in the USA (including Puerto Rico or other US territories), and employment in

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the 24 months before TB diagnosis. Social characteristics collected during TB case management included self-reported history of ever having been incarcerated, ever having been homeless (available since 2004), ever abusing alcohol, injection drug use (IDU) ever, or other illicit drug use (non-IDU) ever. Self-reported history of treatment for alcohol or drug use was included in these categories. DOHMH staff attempted to ascertain HIV status from every TB patient through a combination of patient self-report, chart review and/or testing. For this analysis, persons were categorized as known to be HIV-infected if there was a record of a positive test result in the TB registry or a match with the HIV registry, and not known to be HIV-infected if the TB registry data had a documented negative result or HIV status was indicated as unknown in the TB registry and there was no match to the HIV registry.

Clinical characteristics examined included site of TB disease, initial chest radiograph status in persons with pulmonary TB, and positive culture for *Mycobacterium tuberculosis* status. To explore the use of non-standard medication regimens and how this may have been influenced by hepatitis infection status, a marker for treatment with a liver-sparing regimen was included, defined as ever having been prescribed an aminoglycoside, cycloserine, capreomycin or a fluoroquinolone. Additionally a variable was created to indicate whether the patient was started on the standard four-drug regimen of rifampin, isoniazid, pyrazinamide and ethambutol (RIPE) within the first 7 days after treatment initiation. Treatment outcome measures were mutually exclusive and included: completed treatment, died before treatment initiation or completion, and 'other', comprising administratively closed, adverse reaction leading to treatment discontinuation, lost, moved, or refused treatment.

For persons who died before treatment completion, underlying cause of death was obtained from the cross-matched NYC vital statistics mortality data. ICD-10 codes were grouped by cause into the following categories: TB (A16-A19); TB and HIV (B20·0); HIV (B20·1-B24); hepatitis-related, including viral hepatitis (B16-B19), liver cancer (C22), and cirrhosis (K70, K73–74); and other, including all other recorded ICD-10 codes.

Statistical analysis

Characteristics and TB outcome measures were stratified by viral hepatitis status. Proportions were calculated excluding missing values. Pearson's χ^2 or Fisher's exact tests were used to obtain P values separately comparing persons with TB and HCV or HBV infection to persons with TB and no viral hepatitis report. Given the large proportion of persons with viral hepatitis infection who also had HIV, and the known impact of HIV on TB outcomes, the results were further stratified by HIV status to examine characteristics associated with viral hepatitis infection, independent of HIV infection. Sensitivity analyses were performed excluding patients reported with both HCV and HBV infection, and excluding persons with unknown HIV status. Analyses were conducted using SAS v. 9·2 (SAS Institute Inc., USA). This project was given a non-human subjects research determination by the NYC DOHMH Institutional Review Board.

RESULTS

Study population

Between 1 January 2000 and 31 December 2010, 10905 cases of TB were diagnosed in NYC residents. The study population consisted of 9512 persons with TB after excluding those whose TB care ended after 31 December 2010 ($N = 436$), persons with a TB diagnosis prior to the study period and subsequent TB episodes for persons with multiple TB diagnoses during the study period ($N = 188$), persons aged <18 years ($N = 605$), and persons with MDR-TB ($N = 164$) (Fig. 1).

HCV and HBV infection in persons with TB

Of 9512 persons with TB, HCV infection was reported in 4·2% ($n = 400$) and HBV infection was reported in 3·7% ($n = 350$); 25 persons (0·3%) had both HCV and HBV infection (Fig. 1). The proportion male in TB patients with HCV infection was larger than in TB patients without a viral hepatitis report (72% *vs.* TB only 61%, $P < 0·01$) (Table 1). The majority (83%) of persons with HCV infection and TB were US born, compared to one-quarter of those with TB only ($P < 0·01$). The proportion reporting a history of homelessness, incarceration, alcohol abuse, IDU, and non-IDU was larger in TB patients with HCV infection than in TB patients without a viral hepatitis report.

The proportion starting on RIPE in TB patients with HCV infection was smaller than in TB patients without a viral hepatitis report (85% *vs.* 90%, $P < 0·01$) and the proportion treated with a liver-sparing regimen in TB

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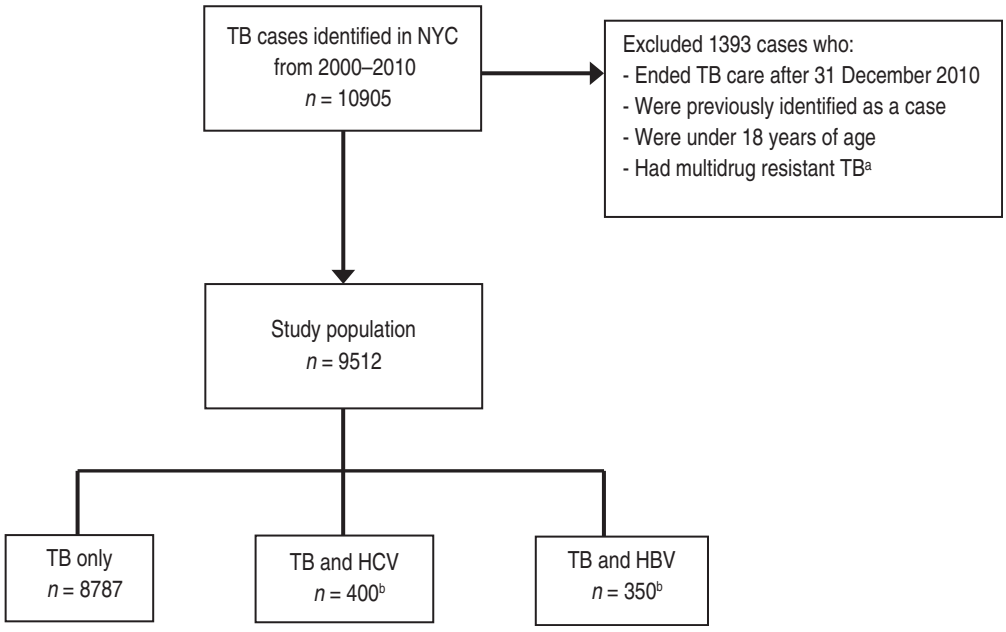

Fig. 1. Study population. [a]Multidrug-resistant tuberculosis is defined as resistance to at least isoniazid and rifampin. [b]Twenty-five persons had both HCV and HBV infection and are included in both groups.

patients with HCV infection was larger than in TB patients without a viral hepatitis report (28% *vs.* 16%, $P < 0{\cdot}01$) (Table 1). The proportion completing anti-TB treatment in TB patients with HCV infection was smaller than in TB patients without a viral hepatitis report (75% *vs.* 86%, $P < 0{\cdot}01$). Death before TB treatment completion was more common in TB patients with HCV infection than in TB patients without a viral hepatitis report (21% *vs.* 9%, $P < 0{\cdot}01$). For TB patients with HCV infection who died before treatment completion, the majority (56%) were indicated in vital statistics data as having died of HIV-related causes.

TB patients with HBV infection were not statistically different from TB patients without a viral hepatitis report on most demographic and social characteristic measures, with the exception of a history of homelessness (8% *vs.* 5%, $P = 0{\cdot}04$), IDU (6% *vs.* 3%, $P < 0{\cdot}01$), and non-IDU (18% *vs.* 8%, $P < 0{\cdot}01$) (Table 2). These observed differences in homelessness and IDU between TB patients with HBV infection and TB patients with no viral hepatitis report did not persist when persons reported with both HCV and HBV infections were removed from the sensitivity analysis (data not shown). The only statistically significant difference in clinical characteristics between TB patients without a viral hepatitis report and TB patients with HBV infection was in the proportion of patients with an abnormal chest X-ray (92% *vs.* 95%, $P = 0{\cdot}02$). A greater proportion of TB patients with HBV infection died before treatment completion (13% *vs.* 9%, $P < 0{\cdot}01$). The majority of deaths in persons with HBV infection were HIV-related (51%) according to vital statistics data.

Stratification by HIV status

HIV infection was present in 56% of TB patients with HCV infection and 34% of TB patients with HBV infection, compared to 13% of TB patients without a viral hepatitis report (Tables 1 and 2). While 8% of all TB patients had a viral hepatitis infection, 23% of TB patients with HIV had a viral hepatitis infection. Most demographic and social characteristic differences between TB patients with HCV infection and TB patients without a viral hepatitis report persisted when stratified by HIV infection status (Table 1). Conversely, stratification by HIV status removed most of the differences between TB patients with HBV infection and TB patients without a viral hepatitis report (Table 2).

Across HIV strata the significant difference in the proportion of TB patients with HCV who died before TB treatment completion persisted (18% *vs.* 8% in those not known to be HIV-infected, $P < 0{\cdot}01$; 24% *vs.* 15% in those HIV-infected, $P < 0{\cdot}01$) (Table 1). Of TB patients with HCV infection who died before TB treatment completion, none with known HIV

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Table 1. *Characteristics of TB patients with hepatitis C virus (HCV) infection, New York City, 2000–2010*

	Total (%)			Not known HIV-infected[a] (%)			Known HIV-infected (%)		
	TB only	TB/HCV	*P* value	TB only	TB/HCV	*P* value	TB only	TB/HCV	*P* value
Total[b]	8787	400	—	7624	176	—	1163	224	—
Male sex	5335 (61)	286 (72)	<0·01	4546 (60)	127 (72)	<0·01	789 (68)	159 (71)	0·35
Age group, yr									
18–44	4792 (55)	124 (31)	<0·01	4073 (53)	36 (20)	<0·01	719 (62)	88 (39)	<0·01
45–64	2441 (28)	238 (60)	<0·01	2025 (27)	106 (60)	<0·01	416 (36)	132 (59)	<0·01
⩾65	1554 (18)	38 (10)	<0·01	1526 (20)	34 (19)	0·82	28 (2)	4 (2)	0·81
US-born[c]	2276 (26)	328 (83)	<0·01	1655 (22)	120 (69)	<0·01	621 (54)	208 (94)	<0·01
Employed in 24 months before TB diagnosis[d]	3766 (44)	60 (15)	<0·01	3380 (45)	41 (24)	<0·01	386 (34)	19 (9)	<0·01
Ever homeless[e]	248 (5)	75 (30)	<0·01	162 (4)	28 (22)	<0·01	86 (16)	47 (40)	<0·01
Ever incarcerated[f]	149 (39)	38 (86)	<0·01	85 (28)	13 (72)	<0·01	64 (84)	25 (96)	0·11
Ever abused alcohol[g]	1398 (16)	209 (54)	<0·01	1045 (14)	81 (47)	<0·01	353 (31)	128 (60)	<0·01
Ever injection drug use[h]	231 (3)	157 (41)	<0·01	86 (1)	47 (27)	<0·01	145 (13)	110 (51)	<0·01
Ever non-injection drug use[i]	727 (8)	218 (57)	<0·01	381 (5)	69 (40)	<0·01	346 (31)	149 (71)	<0·01
Clinical characteristics									
Any pulmonary TB	6658 (76)	332 (81)	0·03	5764 (76)	144 (82)	0·06	894 (77)	178 (79)	0·40
Abnormal chest X-ray[j]	6293 (95)	287 (90)	<0·01	5546 (97)	137 (96)	0·77	747 (84)	150 (85)	0·67
Cavitary chest X-ray	1375 (22)	39 (14)	<0·01	1291 (23)	28 (20)	0·44	84 (11)	11 (7)	0·16
Started on RIPE	7899 (90)	340 (85)	<0·01	6855 (90)	149 (85)	0·02	1044 (90)	191 (85)	0·05
Ever on liver-sparing regimen[k]	1415 (16)	113 (28)	<0·01	1134 (15)	41 (23)	<0·01	281 (24)	72 (32)	0·01
TB treatment outcomes									
Completed treatment	7520 (86)	300 (75)	<0·01	6607 (87)	138 (78)	<0·01	913 (79)	162 (72)	0·04
Died before treatment completion	772 (9)	85 (21)	<0·01	598 (8)	31 (18)	<0·01	174 (15)	54 (24)	<0·01
HIV-related death[l]	100 (15)	34 (43)	<0·01	0	0	1·0	100 (63)	34 (65)	0·47
TB-related death	147 (21)	5 (6)	<0·01	140 (26)	5 (18)	0·35	7 (4)	0	0·90
HIV-and TB-related death	26 (4)	10 (13)	<0·01	1 (1)	0	1·0	25 (16)	10 (19)	0·46
Hepatitis-related death	16 (2)	7 (9)	<0·01	16 (3)	7 (25)	<0·01	0	0	1·0
Other cause of death	400 (58)	24 (30)	<0·01	373 (70)	16 (57)	0·23	27 (17)	8 (15)	0·90
Other reason for case closure	495 (6)	15 (4)	0·09	419 (6)	7 (4)	0·38	76 (7)	8 (4)	0·09

[a] Not known to be HIV-infected includes patients with a documented negative result and patients with unknown HIV status.
[b] Percentages exclude missing values.
[c] Country of birth was known for: $n = 8753$ (TB only), $n = 397$ (TB/HCV), $n = 7595$ (not known HIV-infected, TB only), $n = 175$ (not known HIV-infected, TB/HCV), $n = 1158$ (known HIV-infected, TB only), $n = 222$ (known HIV-infected, TB/HCV).
[d] Employed in 24 months before TB diagnosis was known for: $n = 8614$ (TB only), $n = 389$ (TB/HCV), $n = 7485$ (not known HIV-infected, TB only), $n = 174$ (not known HIV-infected, TB/HCV), $n = 1129$ (known HIV-infected, TB only), $n = 215$ (known HIV-infected, TB/HCV).
[e] Homelessness variable was available for TB cases starting in 2004. Homelessness was known for: $n = 4739$ (TB only), $n = 248$ (TB/HCV), $n = 4216$ (not known HIV-infected, TB only), $n = 129$ (not known HIV-infected, TB/HCV), $n = 523$ (known HIV-infected, TB only), $n = 119$ (known HIV-infected, TB/HCV).
[f] Incarceration was known for: $n = 382$ (TB only), $n = 44$ (TB/HCV), $n = 306$ (not known HIV-infected, TB only), $n = 18$ (not known HIV-infected, TB/HCV), $n = 76$ (known HIV-infected, TB only), $n = 26$ (known HIV-infected, TB/HCV).
[g] Alcohol abuse was known for: $n = 8561$ (TB only), $n = 385$ (TB/HCV), $n = 7431$ (not known HIV-infected, TB only), $n = 173$ (not known HIV-infected, TB/HCV), $n = 1130$ (known HIV-infected, TB only), $n = 212$ (known HIV-infected, TB/HCV).
[h] Injection drug use was known for: $n = 8560$ (TB only), $n = 387$ (TB/HCV), $n = 7434$) (not known HIV-infected, TB only), $n = 173$ (not known HIV-infected, TB/HCV), $n = 1126$ (known HIV-infected, TB only), $n = 214$ (known HIV-infected, TB/HCV).
[i] Non-injection drug use was known for: $n = 8565$ (TB only), $n = 385$ (TB/HCV), $n = 7436$ (not known HIV-infected, TB only), $n = 174$ (not known HIV-infected, TB/HCV), $n = 1129$ (known HIV-infected, TB only), $n = 211$ (known HIV-infected, TB/HCV).
[j] Chest X-ray status among those with a pulmonary site of disease.
[k] Liver-sparing regimen defined as ever having been prescribed an aminoglycoside, cycloserine, capreomycin, or a fluoroquinolone.
[l] Cause of death from match with vital statistics death certificate data.

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Table 2. *Characteristics of TB patients with hepatitis B virus (HBV) infection, New York City, 2000–2010*

	Total (%)			Not known HIV-infected[a] (%)			Known HIV-infected (%)		
	TB only	TB/HBV	*P* value	TB only	TB/HBV	*P* value	TB only	TB/HBV	*P* value
Total[b]	8787	350		7624	231	—	1163	119	
Male sex	5335 (61)	249 (71)	<0·01	4546 (60)	161 (70)	<0·01	789 (68)	88 (74)	0·17
Age group, yr									
18–44	4792 (55)	196 (56)	0·59	4073 (53)	118 (51)	0·48	719 (62)	78 (66)	0·43
45–64	2441 (28)	113 (32)	0·07	2025 (27)	74 (32)	0·06	416 (36)	39 (33)	0·52
⩾65	1554 (18)	41 (12)	<0·01	1526 (20)	39 (17)	0·24	28 (2)	2 (2)	1·00
US-born[c]	2276 (26)	88 (25)	0·72	1655 (22)	24 (10)	<0·01	621 (54)	64 (54)	0·97
Employed in 24 months before TB diagnosis[d]	3766 (44)	142 (41)	0·40	3380 (45)	107 (47)	0·60	386 (34)	35 (30)	0·42
Ever homeless[e]	248 (5)	20 (8)	0·04	162 (4)	5 (3)	0·49	86 (16)	15 (23)	0·18
Ever incarcerated[f]	149 (39)	5 (28)	0·34	85 (28)	3 (23)	0·71	64 (84)	2 (40)	0·04
Ever abused alcohol[g]	1398 (16)	62 (18)	0·46	1045 (14)	23 (10)	0·08	353 (31)	39 (33)	0·69
Ever injection drug use[h]	231 (3)	20 (6)	<0·01	86 (1)	3 (1)	0·84	145 (13)	17 (14)	0·64
Ever non-injection drug use[i]	727 (8)	62 (18)	<0·01	381 (5)	13 (6)	0·72	346 (31)	49 (42)	0·02
Clinical characteristics									
Any pulmonary TB	6658 (76)	281 (80)	0·05	5764 (76)	195 (84)	<0·01	894 (77)	86 (72)	0·26
Abnormal chest X-ray[j]	6293 (95)	256 (92)	0·02	5546 (97)	187 (97)	0·99	747 (84)	69 (81)	0·51
Cavitary chest X-ray	1375 (22)	51 (20)	0·32	1291 (23)	44 (24)	0·94	84 (11)	7 (10)	0·78
Started on RIPE	7899 (90)	319 (91)	0·45	6855 (90)	211 (91)	0·48	1044 (90)	141 (92)	0·71
Ever on liver-sparing regimen[k]	1415 (16)	69 (20)	0·07	1134 (15)	36 (16)	0·77	281 (24)	33 (28)	0·39
TB treatment outcomes									
Completed treatment	7520 (86)	289 (83)	0·12	6607 (87)	199 (86)	0·82	913 (79)	90 (76)	0·47
Died before treatment completion	772 (9)	46 (13)	<0·01	598 (8)	21 (9)	0·49	174 (15)	25 (21)	0·08
HIV-related death[l]	100 (15)	20 (46)	<0·01	0	0	1·0	100 (63)	20 (83)	0·03
TB-related death	147 (21)	4 (9)	0·11	140 (26)	3 (15)	0·33	7 (4)	1 (4)	1·00
HIV-and TB-related death	26 (4)	2 (5)	0·66	1 (1)	0	1·0	25 (16)	2 (8)	0·53
Hepatitis-related death	16 (2)	5 (12)	<0·01	16 (3)	5 (25)	<0·01	0	0	1·0
Other cause of death	400 (58)	13 (30)	<0·01	373 (70)	12 (60)	0·63	27 (17)	1 (4)	0·21
Other reason for case closure	495 (6)	15 (4)	0·28	419 (6)	11 (5)	0·63	76 (7)	4 (3)	0·23

[a] Not known to be HIV-infected includes patients with a documented negative result and patients with unknown HIV status.
[b] Percentages exclude missing values.
[c] Country of birth was known for: $n = 8753$ (TB only), $n = 350$ (TB/HBV), $n = 7595$ (not known HIV-infected, TB only), $n = 231$ (not known HIV-infected, TB/HBV), $n = 1158$ (known HIV-infected, TB only), $n = 119$ (known HIV-infected, TB/HBV).
[d] Employed in the 24 months before TB diagnosis was known for: $n = 8614$ (TB only), $n = 343$ (TB/HBV), $n = 7485$, (not known HIV-infected, TB only), $n = 228$ (not known HIV-infected, TB/HBV), $n = 1129$ (known HIV-infected, TB only), $n = 115$ (known HIV-infected, TB/HBV).
[e] Homelessness variable was available for TB cases starting in 2004. Homelessness was known for: $n = 4739$ (TB only), $n = 242$ (TB/HBV), $n = 4216$ (not known HIV-infected, TB only), $n = 177$ (not known HIV-infected, TB/HBV), $n = 523$ (known HIV-infected, TB only), $n = 65$ (known HIV-infected, TB/HBV).
[f] Incarceration was known for: $n = 382$ (TB only), $n = 18$ (TB/HBV), $n = 306$ (not known HIV-infected, TB only), $n = 13$ (not known HIV-infected, TB/HBV), $n = 76$ (known HIV-infected, TB only), $n = 5$ (known HIV-infected, TB/HBV).
[g] Alcohol abuse was known for: $n = 8561$ (TB only), $n = 348$ (TB/HBV), $n = 7431$ (not known HIV-infected, TB only), $n = 230$ (not known HIV-infected, TB/HBV), $n = 1130$ (known HIV-infected, TB only), $n = 118$ (known HIV-infected, TB/HBV).
[h] Injection drug use was known for: $n = 8560$ (TB only), $n = 348$ (TB/HBV), $n = 7434$ (not known HIV-infected, TB only), $n = 230$ (not known HIV-infected, TB/HBV), $n = 1126$ (known HIV-infected, TB only), $n = 118$ (known HIV-infected, TB/HBV).
[i] Non-injection drug use was known for: $n = 8565$ (TB only), $n = 348$ (TB/HBV), $n = 7436$ (not known HIV-infected, TB only), $n = 230$ (not known HIV-infected, TB/HBV), $n = 1129$ (known HIV-infected, TB only), $n = 118$ (known HIV-infected, TB/HBV).
[j] Chest X-ray status in those with a pulmonary site of disease.
[k] Liver-sparing regimen defined as ever having been prescribed an aminoglycoside, cycloserine, capreomycin, or a fluoroquinolone.
[l] Cause of death from match with vital statistics death certificate data.

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infection died of liver-related causes while 25% not known to be HIV-infected died of liver-related causes based on death certificate data. In TB patients with HBV infection, no significant differences were observed in clinical characteristics or TB treatment outcomes when stratified by HIV status (Table 2).

HIV status was unknown for 29% of TB patients without a viral hepatitis report, 13% of TB patients with HCV infection, and 22% of TB patients with HBV infection. Excluding patients with unknown HIV status from the group not known to be HIV-infected had little impact on the HIV-stratified analysis. The only exception was that, when stratified by HIV status, there was no longer a significant difference in hepatitis-related deaths between TB patients with HCV or HBV infection compared to TB patients without a viral hepatitis report (data not shown).

DISCUSSION

The proportion of TB patients with a report of HCV infection was nearly twice the estimated prevalence of HCV infection in all NYC residents (4·2% *vs.* 2·4%) [25] and the proportion of TB patients with a report of HBV infection was more than three times the estimated NYC prevalence (3·7% *vs.* 1·2%) [23]. Campo *et al.* found similar results in Seattle, reporting a HCV prevalence of 3·6% in TB patients [12], while studies outside the USA have found a higher prevalence of both HCV and HBV infection in TB patients than was observed in NYC [8, 13–21], highlighting the variation in the distribution of TB and viral hepatitis globally.

TB patients with HCV infection had different social characteristics than TB patients without a report of viral hepatitis infection. A history of incarceration, IDU, and homelessness were found to be associated with HCV infection in other studies and the present study [12, 13, 16, 18]; we additionally found that HCV infection was associated with non-IDU and with unemployment in the 24 months before TB diagnosis. These characteristics are also considered traditional risk factors for TB disease, particularly in the US-born population of NYC [22]. This overlap of risk factors may help to explain our finding that the majority of TB cases with HCV infection were born in the US, a result that is consistent with the one other US study of HCV infection in TB patients [12]. Similar to previous studies, we found that IDU and non-IDU were more common in TB patients with HBV infection [18, 20], although once stratified by HIV status, only the association with non-IDU remained. These findings suggest that TB patients with HCV infection, in particular, face barriers that are known to make TB treatment completion more difficult.

More persons with TB and HCV infection were treated with a liver-sparing regimen compared to TB patients without a viral hepatitis report; however, we did not observe a difference in the use of these regimens in persons with TB and HBV infection. Although we were not able to determine the specific reasons for treatment with an alternative regimen, these medications are typically used when hepatotoxicity is a concern or when hepatic dysfunction is present. Most studies assessing the impact of HCV infection on hepatotoxicity have found that HCV co-infected TB patients were more likely to experience hepatic dysfunction than those without HCV infection [8, 11, 13, 14, 21]. The literature is less clear about the impact of HBV infection [8–10, 13, 14, 21].

The proportion of TB patients with HCV infection, regardless of HIV infection status, that died before TB treatment completion was larger than in TB patients with no report of viral hepatitis infection. Hepatitis-related deaths, based on death certificate data, did appear to differ by HIV status, but more detailed review of the circumstances behind these deaths is beyond the scope of this paper. This finding stands in contrast to the other US study, which found that death before treatment completion was not different between TB patients with and without HCV [12]. We also found that more persons with HBV died before TB treatment completion compared to persons with TB only; however, this difference was not statistically significant when stratified by HIV status. These findings support those of Sirinak *et al.*, who found that HBV infection was not associated with death in HIV-positive TB cases [13]. In sensitivity analysis, when patients with unknown HIV status were excluded, we found that the higher proportion of TB patients with HBV or HCV who died from hepatitis-related causes was no longer significant. Ascertaining HIV status may not have been possible if patients died soon after TB diagnosis, which may indicate delays in care seeking or diagnosis.

There are some limitations to our analysis. Results were based on the deterministic match of NYC surveillance registries and did not include a manual review of possible matches (i.e. name, date of birth, and social security number were not compared across individual linked records) to verify that they were true

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matches. Therefore, TB patients could have been misclassified with respect to HCV, HBV, or HIV status; however, because the match was conservative, any misclassification from the match likely resulted in underestimates of co-infection. Our estimates of the proportion of TB patients with a report of HCV and HBV infection are likely lower than the true prevalence estimate, as viral hepatitis surveillance data only contains positive test results and therefore, the denominator of our estimates is all persons with TB rather than all persons with TB who were tested for viral hepatitis infection. We were unable to determine which of those persons reported with only a positive HCV antibody result had chronic HCV. It is estimated that between 20% and 30% of HCV antibody-positive persons are RNA negative because of a resolved infection or a false-positive result [29]; this may have resulted in overestimation of the prevalence of HCV infection in our study population. Additionally, cause of death was obtained from death certificate data, which can be subject to error; HCV infection, for example, may be under-documented on death certificates [30]. Finally, some of the social characteristic variables had substantial missing data, were self-reported and were not collected consistently over the entire study period.

Despite its limitations, this descriptive analysis has several strengths. The cross-match of multiple surveillance databases and vital statistics mortality records covering more than a decade allowed for ascertainment of reported viral hepatitis and HIV infection status, as well as cause of death in those who died before TB treatment completion. In addition, the large sample size and rich detail available in the TB database obtained through the case management of every TB case allowed us to describe characteristics and treatment outcomes for TB patients with HCV and HBV infection.

Public health implications

Viral hepatitis and HIV infection status should be ascertained for all TB patients concurrent with treatment initiation, if not already known. Given the recent advances in curative antiviral treatment for HCV [31, 32], additional research is needed to identify interactions between these drugs and the drugs used to treat TB, as well as the optimal timing and choice of hepatitis therapy during TB treatment. Guidelines to assist clinicians in making these decisions may improve TB treatment outcomes and prevent deaths.

In addition to those diagnosed with TB disease, clinicians should also consider viral hepatitis screening for the much larger group of individuals diagnosed with latent TB infection. Especially when there is less clinical urgency to treat an individual's TB infection, optimal clinical guidelines are needed to clarify which infection (TB or viral hepatitis) should be treated first or whether simultaneous treatment should be pursued.

In this population, about half of persons with TB disease and viral hepatitis infection were also known to have HIV infection. This demonstrates that there is a small, but highly vulnerable population experiencing a syndemic of multiple infectious diseases. Of those with TB and viral hepatitis infection who died before treatment completion, 50% died of HIV-related causes. These findings further highlight the importance of knowing a TB patient's HIV status and reinforce the importance of efforts that NYC and other jurisdictions are making to test all TB patients for HIV and connect HIV-infected persons to care and treatment [33].

The persistent differences in outcomes for TB patients with HCV across HIV strata may be explained by the large proportion of patients with HCV and social risk factors including a history of substance use, homelessness, unemployment, and incarceration. These factors, as well as psychiatric illness, are well-documented as frequently co-occurring in persons with HCV [34, 35], and can create barriers to treatment for individuals with TB and HCV infection. Achieving outcomes for TB patients with HCV infection that are equivalent to those seen for patients without viral hepatitis infection will require more intensive interventions to address these underlying factors.

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DECLARATION OF INTEREST

None.

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