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High prevalence of hepatitis C infection among multidrug-resistant tuberculosis patients

To the Editor:

In "Integrating HCV testing with HIV programs improves hepatitis C outcomes in people who inject drugs: A cluster-randomized trial",[1] the authors studied an intervention that integrated HCV testing and education into HIV services across India. In our opinion, many national tuberculosis (TB) programs should also consider integrating HCV testing. TB or the highly resistant variant of the disease, multidrug-resistant (MDR) TB, is generally not considered a risk factor for HBV or HCV infection, except in those who are co-infected with HIV or who are intravenous drug users. Routine, systematic testing for HCV is rare in patients with MDR-TB and is not currently recommended in World Health Organization guidelines for MDR-TB treatment.

The endTB Observational Study (NCT02754765) is a study of patients receiving a bedaquiline- or delamanid-containing regimen for rifampicin-resistant/MDR-TB at sites in 17 countries: Armenia, Bangladesh, Belarus, Democratic People's Republic of North Korea, Ethiopia, Kenya, Georgia, Haiti, Indonesia, Kazakhstan, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Peru, South Africa, Vietnam.[2] Patients were eligible for inclusion if they received a regimen containing either bedaquiline or delamanid at an endTB site and provided informed consent to allow their clinical data to be analyzed. A study protocol guided data collection, but not treatment, across sites. During the study time period, patients were generally treated with bedaquiline or delamanid when a regimen of at least 4 likely effective drugs could not be constructed due to resistance or toxicity. Most patients received longer individualized treatment regimens according to national TB program guidelines.

We examined data from the 10 countries that enrolled at least 30 patients in the endTB Observational Study between April 1, 2015 and December 31, 2017. A positive HBsAg test was considered evidence of chronic or acute hepatitis B infection. A positive hepatitis C antibody (ELISA or point-of-care rapid test kit) or positive PCR/genotype was considered evidence of hepatitis C infection.

Uptake of screening was high overall; in all countries except for Georgia, the percentage of patients screened was greater than 90% (see Table 1). HCV prevalence was most common among MDR-TB patients in Eastern Europe (previously reported in Georgia[3]) and was also high in several countries outside of Eastern Europe: Kazakhstan, Pakistan and Myanmar. In these 6 countries, HCV prevalence was generally much higher than HBV prevalence and also higher than previously reported estimates in the general population. HBV prevalence exceeded 20% in only 1 country, Myanmar.

It is unclear what is driving HCV infection in MDR-TB patients. HCV is associated with unsafe injection practices, unscreened blood transfusions, injection drug use, mother-to-child transmission, tattooing/body piercing and needlestick injuries in health care workers.[4] Injection drug use could be a contributing factor to the elevated prevalence of HCV in some countries in this study. Eastern Europe and Central Asia are thought to have to have the highest prevalence of injection drug use globally.[5] Poor sterile technique in the therapeutic injection of anti-TB drugs may be an important unrecognized factor contributing to HCV transmission in patients with TB, just as injection of anti-schistosomal treatment was for transmission of HCV in Egypt.[6] For decades, intramuscular injections of streptomycin, amikacin, kanamycin and capreomycin have been a mainstay of TB and MDR-TB treatment; most patients in this cohort had previously received lengthy injectable-containing TB treatment regimens. Recent meta-analyses of HCV epidemiology in Pakistan[7] and Central Asia[8] indicate that health care-related exposures such as therapeutic injections and intravenous infusions could be a more important risk factors in these countries than injection drug use and other community-based exposures.

Chronic HBV or HCV infection is associated with drug-induced liver injury and poor outcomes during first-line TB treatment.[9,10] Similar studies have not been performed in patients with MDR-TB, but our experience indicates that co-infected patients with MDR-TB have a similar or greater risk of drug-induced liver injury during treatment (unpublished endTB data). In patients with chronic HBV infection who are undergoing treatment with first-line TB drugs, anti-viral therapy for HBV can prevent liver injury.[11] Direct-acting antivirals for HCV appear to be well tolerated and may have a similar beneficial effect on MDR-TB treatment outcomes.

These results support the integration of routine HBV and HCV screening into national MDR-TB treatment protocols in high prevalence countries. Further studies are needed to determine HCV prevalence in patients with TB and MDR-TB in additional

Table 1. Prevalence of hepatitis C and B in patients with multidrug-resistant tuberculosis enrolled in the endTB observational study.

Country (N = 1,751)	Patients with HCV testing, n (%)	HCV infection* among tested, n (%)	Patients with HBV testing, n (%)	HBsAg among tested, n (%)
Armenia (n = 106)	106 (100)	27 (25)	101 (95)	0 (0)
Bangladesh (n = 208)	208 (100)	0 (0)	208 (100)	9 (4)
Belarus (n = 75)	75 (100)	22 (29)	74 (99)	3 (4)
Ethiopia (n = 42)	42 (100)	1 (2)	42 (100)	2 (5)
Georgia (n = 290)	232 (80)	70 (30)	216 (74)	13 (6)
Kazakhstan (n = 369)	338 (92)	52 (15)	337 (91)	18 (5)
Lesotho (n = 163)	154 (94)	0 (0)	149 (91)	9 (6)
Myanmar (n = 40)	39 (98)	4 (10)	39 (98)	8 (21)
Pakistan (n = 214)	214 (100)	24 (11)	214 (100)	3 (1)
Peru (n = 159)	156 (98)	0 (0)	157 (99)	1 (1)

*12 additional patients, 2 from Kazakhstan and 10 from Georgia, had a history of hepatitis C infection noted in their medical record, but did not have a laboratory result. These patients were not included in the reported prevalence estimates.

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countries, and to develop best treatment practices for HCV in patients with TB and MDR-TB. Increasing attention to modifiable risk factors such as nosocomial transmission and safe injection practices, as well as access to screening and treatment in patients with TB and MDR-TB, may be an important part of the global strategy to eliminate HCV.

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Conflict of interest
The endTB Consortium coordinated donations of delamanid (Otsuka Pharmaceutical) and bedaquiline (Janssen) to be used for treatment by some of the patients included in the endTB Observational Study. All authors report no additional potential conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
Analysis: MFF, HH, CDM; Conception and writing: KJS, MFF, CH, HH, UK, CDM.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.10.018.

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Reply to: 'High prevalence of hepatitis C infection among multidrug-resistant tuberculosis patients'

To the Editor:

We agree with Seung *et al.*[1] that integrating HCV testing and treatment into existing programs will be critical both for achieving hepatitis C elimination and for the management of other conditions while simultaneously creating efficiencies in the delivery of health care. Our integrated care center (ICC) model for people who inject drugs (PWID) in India was focused on integrating essential infectious disease and harm reduction services in venues tailored to the needs of PWID.[2] While the focus of the results described in the *Journal of Hepatology*[3] was on integration of HCV testing with existing HIV and harm reduction services, it is important to note that other services were offered at the ICCs including screening for tuberculosis and management of sexually transmitted infections.

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