Overcoming challenges in TB care: from policy to practice

Higher rate of hepatotoxicity and lower favorable MDR-TB treatment outcomes in patients co-infected with hepatitis C: Results from the endTB study

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9th Regional TB Symposium
Kyiv, Ukraine 5 – 6 March 2020

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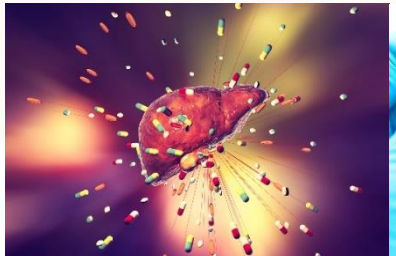
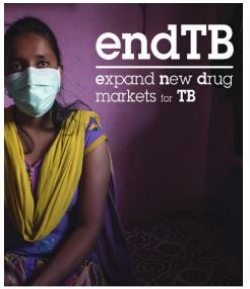
Background

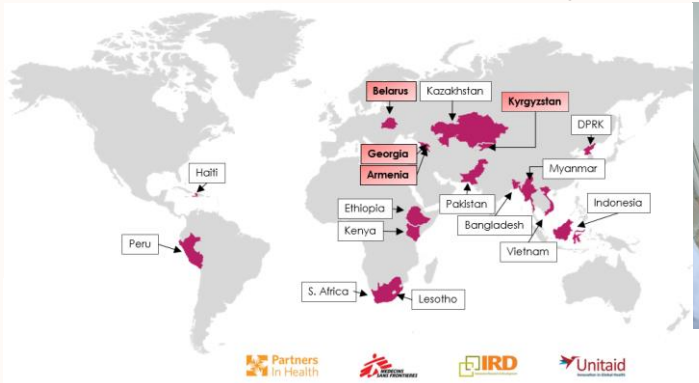
- Hepatotoxicity is common during MDRTB treatment
- Many anti-TB drugs possibly related
- Other possible causes: Hepatitis (A, B, C), excess alcohol consumption, other drugs including nevirapine in HIV-positive patients
- Hepatitis C is highly prevalent in eastern Europe
- Effect of hepatitis C co-infection on MDR-TB treatment outcome is little known today



Methods



- **Population:** all patients who started MDR-TB treatment with bedaquiline or delamanid between April 1st, 2015 and June 30th, 2018 in Armenia, Georgia, Belarus and Kyrgyzstan
- **Hepatotoxicity** = AST or ALT > 5 times upper limit of normal
- **Monitoring schedule** included baseline and monthly liver function tests (AST, ALT)



Results - Characteristics

N=509	Total n (%)
Median age [IQR]	38 [29 – 48]
Female	106 (20.8)
BMI < 18 kg/m^2	112 (22.5)
Diabetes mellitus	49 (9.7)
HIV infection	43 (8.4)
Hepatitis B	17 (3.5)
Hepatitis C	126 (24.8)

Past TB 2nd-line drugs	386 (75.8)
Bilateral disease	333 (67.1)
Cavitary disease	251 (52.4)
Resistance profile	
MDR-TB + FQ resistance	120 (23.6)
XDR-TB	237 (46.6)
Pyrazinamide in initial regimen	107 (21.7)

Results - Hepatotoxicity

- Clinically relevant hepatotoxicity occurred in **78 (15.3%)** patients
- Median time to first occurrence of hepatotoxicity was **3.7 months [IQR 1.1-9.0]** after treatment initiation
- Incidence of hepatotoxicity:

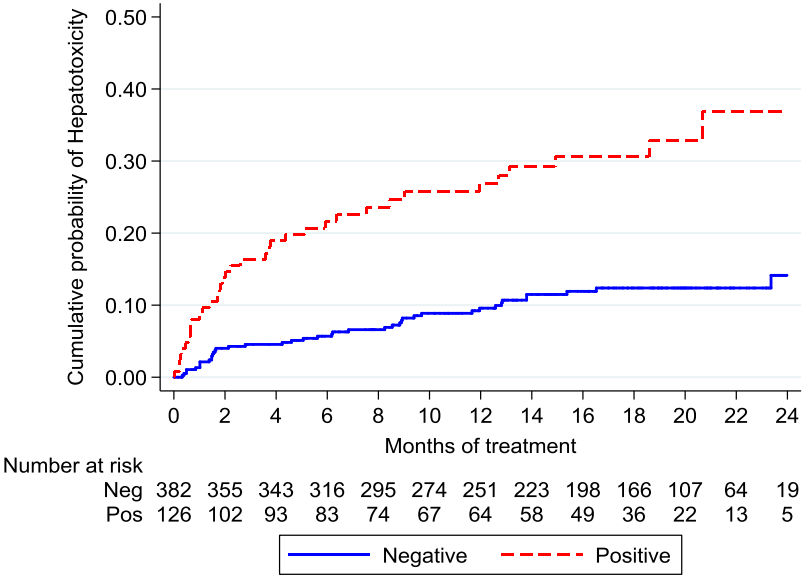
1.1/100 person-months (95%CI, 0.88-1.37)

Results - Hepatotoxicity

	Frequency n/N (%)	Incidence* (95% CI)
Hepatitis C		
Negative	42/382 (11.0%)	0.74 (0.55-1.01)
Positive	36/126 (28.6%)	2.47 (1.78-3.42)

* Incidence /100person-months

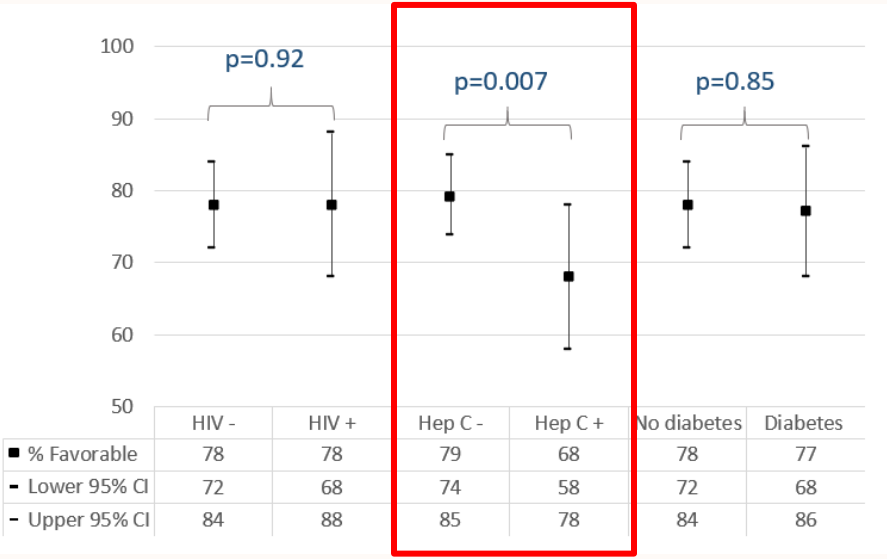
	Adjusted SHR	95% CI
Hepatitis C		
Negative	1	
Positive	3.00	(2.46 – 3.64)



Log-rank test p<0.001

Results – End of treatment outcome

- Favorable end of treatment outcome in **77.6% of patients**



	HIV -	HIV +	Hep C -	Hep C +	No diabetes	Diabetes
% Favorable	78	78	79	68	78	77
Lower 95% CI	72	68	74	58	72	68
Upper 95% CI	84	88	85	78	84	86

Predicted marginal probability of favorable outcome, adjusting for these variables shown and baseline resistance, extensive disease, prior treatment with second line drugs, and toxicity as only indication for BDQ/DLM

Patients with **hepatitis C** were less likely to have a favorable end of treament outcome

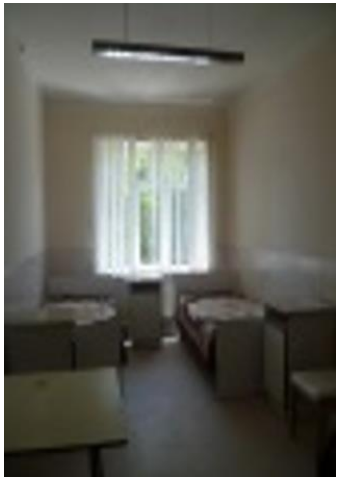
Discussion

- Attribution of the hepatotoxicity to individual drugs is challenging
  - Most of the drugs in the MDR-TB regimen can potentially cause drug-induced liver injury
- Hepatotoxicity is often reversible if caught early
  - Important to monitor with regular testing for an increase in serum liver enzymes
  - Patients co-infected with Hepatitis C should be particularly well monitored
- **Management of hepatotoxicity during MDR-TB treatment:**
  - Stop all drugs including anti-TB drugs and measure liver function tests weekly
  - Treatment may be reintroduced after toxicity is resolved

Discussion

- Patients co-infected with Hepatitis C had lower favorable treatment outcome and should be particularly well monitored
- Until recently, treatment of Hepatitis C was not possible in patients with active tuberculosis
- No contra-indications to the treatment of Hepatitis C with direct acting antivirals (DAAs) in MDR-TB patients treated with second line TB drugs

Treatment with DAAs is possible in MDR-TB patients and should be considered as a priority particularly in patients experiencing hepatotoxicity or at high risk of disease progression



Patients, endTB Teams, National TB Programs, and other collaborators in 17 countries:

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4. DPR Korea
5. Ethiopia
6. Georgia
7. Haiti
8. Indonesia
9. Kazakhstan
10. Kenya
11. Kyrgyzstan
12. Myanmar
13. Lesotho
14. Pakistan
15. Peru
16. S. Africa
17. Vietnam

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