Hepatitis C treatment with direct–acting antiviral drugs in patients with Multidrug-Resistant Tuberculosis in Armenia

The experience of National TB program and MSF

World Health Organization
REGIONAL OFFICE FOR Europe

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HEP C / MDR-TB programme in Armenia (1)

Background

- Hepatotoxicity is a common adverse event during MDR TB treatment

  and (Bastard et all, Bloss et all) and Hepatitis C is a risk factor (Bastard et all, Lee at ell)

- There was no formal documented data on the prevalence of HCV among DR-TB patient in Armenia.
- MSF MDRTB cohort selective data - roughly 6% (as average) of DRTB patients has been exposed and infected with HCV.
- Previously, treatment of Hepatitis C was not possible in patients with active tuberculosis
- New treatments for Hepatitis C with direct acting antivirals (DAA) may be given during tuberculosis treatment

=> important to identify patients with Hepatitis C disease who may benefit from this treatment

HEP C / MDR-TB programme in Armenia (2)

Objectives:

1. To estimate the prevalence of Chronic Hepatitis C infection among MDR-TB patients.

2. To assess the safety, effectiveness of treating Chronic Active Hepatitis C with DAA in patients with MDR-TB.

Steps taken:

2016 screening of MDRTB cases

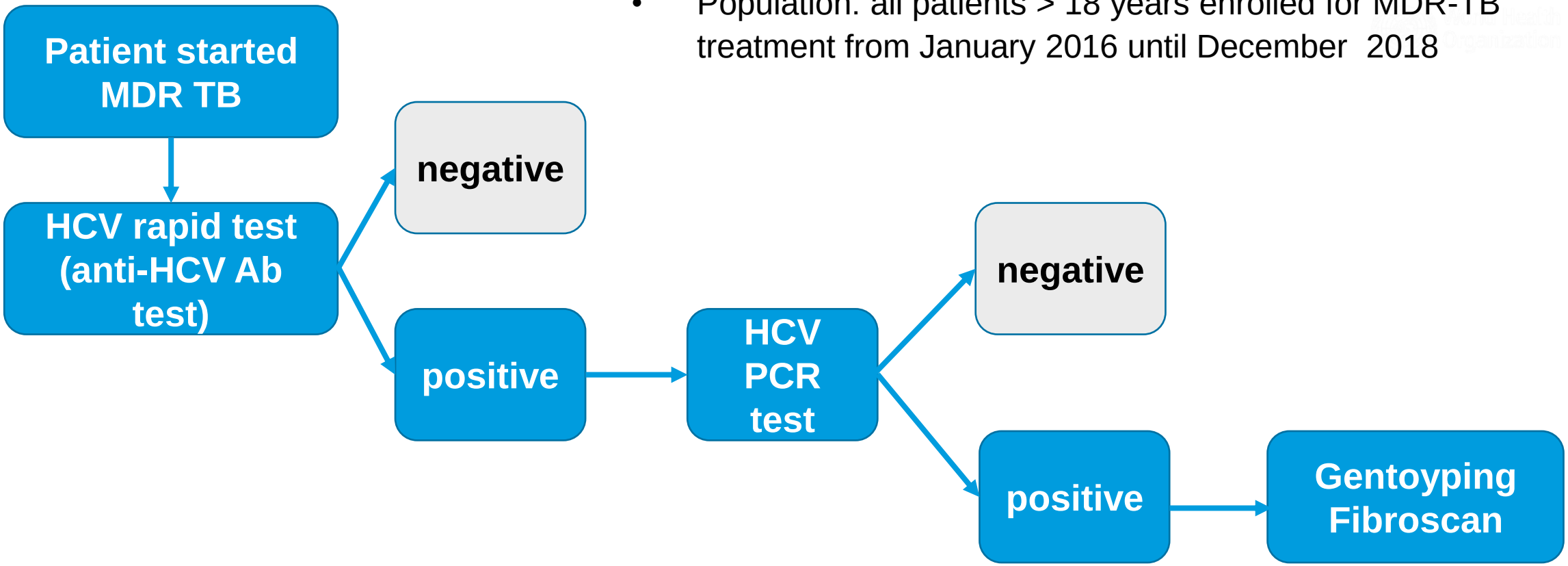
2017 introduction of DDA treatment

2018 March implementation of G-x for HCV viral load

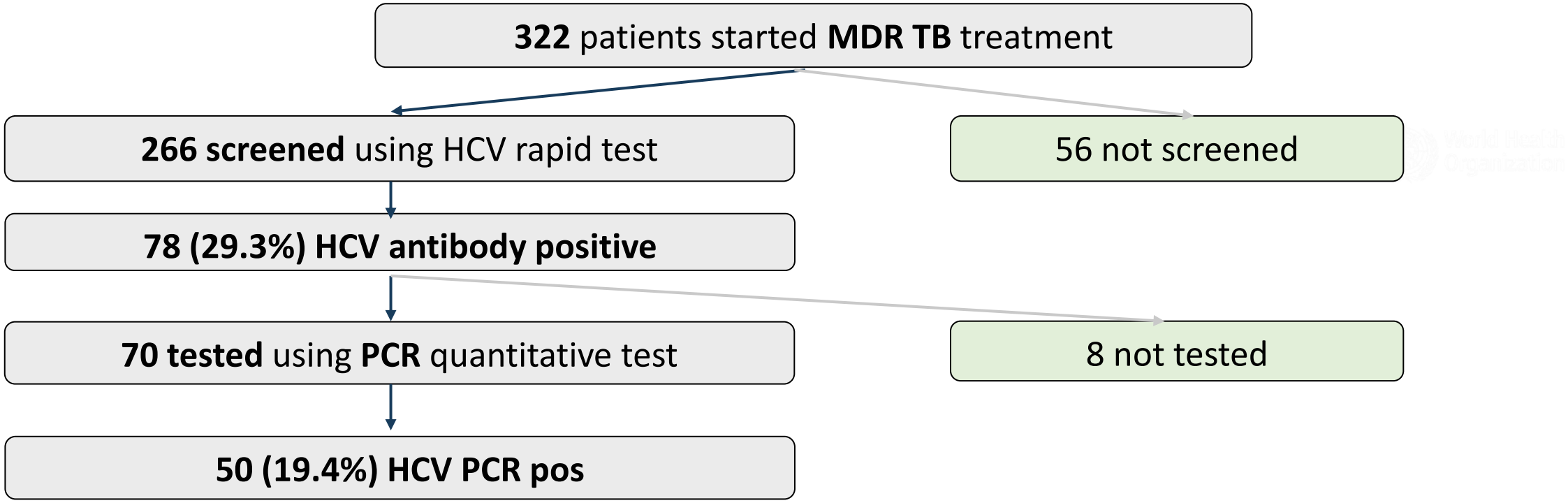
2018 April approval of HCV study on Safety, Effectiveness and Feasibility.

To estimate the prevalence of Chronic Active Hepatitis C among MDR-TB patients

- Population: all patients > 18 years enrolled for MDR-TB treatment from January 2016 until December 2018



Results: HCV prevalence



- The most common genotype among those with active chronic hepatitis C was **1b (40.4%, 19/47)** following by **3a (34.0%, 16/47)**

Eligibility for DAAs

- **After confirmation** of chronic **hepatitis C** infection patient **underwent initial evaluation** and assessed for eligibility.
- **The exclusion criteria for DAAs** were: neoplasia in the terminal stage, advanced/terminal disease, pregnancy/breastfeeding women, uncontrolled psychiatric severe diseases, HIV viral load > 1000 copies/ml, baseline hemoglobin < 9g/dL for regimen containing ribavirin, age below 18 years.
- **At the beginning** of the program treatment with **DAA started in NTCC (7 days hospitalization),** afterwards continued in **ambulatory care** under **DOT or SAT**. **Later** on patients **initiated** treatment at **ambulatory care**.

- Patients in **penitentiary system** were **hospitalized** during the whole treatment duration

Monitoring

Baseline:

- Hepatitis C PCR, serotype
- Hepatitis B testing
- HIV test and CD4
- Clinical and biological evaluations

•Fibroscan:

If advanced disease

- AFP (F3 advanced/F4)
- Ultrasound (If F4)
- Gastroscopy if fibroscan>20kPa and platelets < 150 000

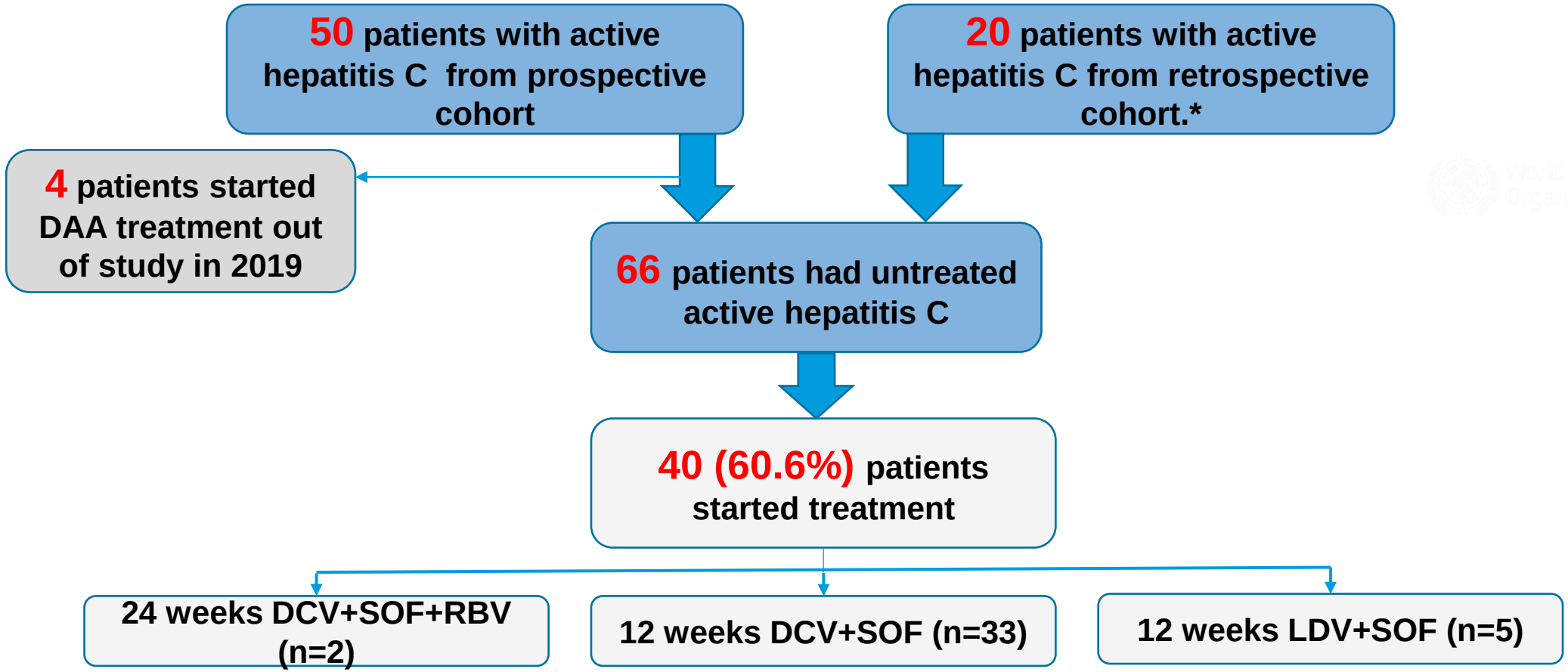
After DAA treatment complete: 12 week sustained viral response (SVR12) HCV PCR or viral load

Monitoring schedule: MDRTB and DAAs treatment

Examination	Monitoring (weeks)								
	baseline	2	4	8	12[1]	16	20	24[2]	12wks post treatment
Medical history	X								
Clinical evaluation	X	X	X	X	X	X	X	X	X
BMI	X				X			X	X
Complete blood count	X		X	X	X	X	X	X	X
Coagulation tests	X								X
Liver enzymes (ALT, AST)	X		X	X	X	X	X	X	X
GGT	X								X
Bilirubin, total	X		X	X	X	X	X	X	X
Creatinine	X		X	X	X	X	X	X	
Albumin if F4	X								
Glucose	X		X	X	X	X	X	X	

[1] for patients on 12 weeks treatment
[2] for patients on 24 weeks treatment

Inclusions for evaluation of safety and effectiveness



* patients were diagnosed with active hepatitis C in 2016, but started MDR TB treatment before study period.
* dose of daclatasvir was increased to 90 mg among patienst whose ART contains efavirenz or nevirapine

Results: DAA treatment outcome

40 patients started DAA
(**30** with MDR TB treatment and 10 after MDR TB treatment completion)

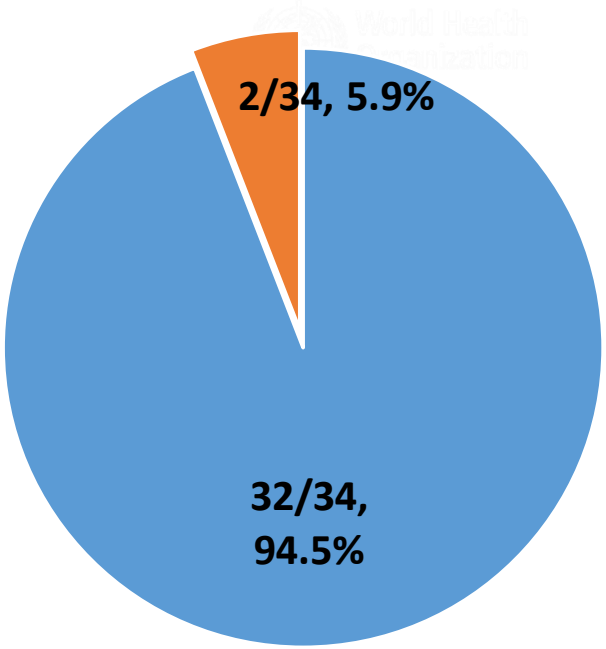
1 was lost to follow up

39 completed course of DAA

2 patients died (lung cancer and HIV), 3 patients left the country

34 reached 12 weeks after end of treatment visit

SVR12 viral response, 94.1%



Treatment success: negative HCV PCR result or viral load concentration below 12IU/mL at 12 weeks after the end of treatment (SVR12).

Treatment failure: positive HCV PCR result or detectable viral load at 12 weeks after end of treatment.

Results: DAA treatment outcome (1)

- HCV PCR result was negative among 31 patients and one patient had HCV PCR positive result with undetectable viral load (<10 IU/ml).
- Two patients failed and had HCV PCR positive test at the end of DAA treatment and at 12 weeks post treatment visit.
- Both of them were male, had genotype 3a, stage F0-F1 fibrosis, received 12 weeks DCV/SOF containing regimen and one of them was HIV positive which was well controlled.

Results: adverse events during the DAA treatment (n=39)

- **2 (5.2%) patients experienced SAE/AE related to DAA**
  - Mild hyperbilirubinemia occurred after two months of DAA start and was still present 12 weeks after end of treatment. The DAA regimen was DCV/SOF/RBV. MDR TB or HCV treatment was not discontinued or stopped temporary due to AE.
  - Severe allergic reaction started 16 days after initiation of DAA. DAA and MDR TB treatments were interrupted twice. However, on antihistamine drugs adverse event resolved and both treatments were completed successfully. Patient was receiving DCV/SOF.

Results: difficulties & strengths

Difficulties	Strengths
Lacking reliable data on hepatitis C in Armenia.	Introduction of the routine HCV screening for MDR TB patients and HCV surveillance system fro MDR TB patients
No National guideline for hepatitis C treatment	Free access to HCV treatment Free accesses to introduced G-xper HCV
Lack of experience to use DAAs including co-administration with other drugs	First experience on co-administration of DAAs and MDR TB drugs
The organization of the medical examinations for smear-positive and imprisoned patients.	Successful incorporation of HCV care in to TB care Successful handover of activity for programmatic management by national TB program

Conclusion (1)

- This is **a first** report **of concomitant use of direct acting antivirals with second line anti-tuberculosis drugs**.
- **A high prevalence of HCV co-infection** among **MDR TB patients** in Armenia (29% HCV antibody positive and 19.4% chronic hepatitis C infection)
- Genotypes **1b** and **3a** are **the most frequent**.
- **Sustained viral suppression** among those tested **was high** (94.1%).
- The c**ombination** of DAAs with second line anti-tuberculosis drugs **is safe**.

Conclusion (2)

- **The implementation** of the program of **integrated HCV/MDR-TB** was **feasible**.
- This is **an easy to access model of care** for MDR TB patients , which was endorsed by both care providers and care recipients.
- The integration of the HCV care in to MDR TB care **did not create much workload** for the doctors.
- The role of the **hepatologist** was important **to support difficult cases.**
- The **main challenge** for the implementation of the integrated HCV/TB care were:
  - The organization of the **medical examinations** for **smear-positive patients** and imprisoned patients outside of TB facility
  - **Identification of private lab and private clinic** for performance of needed investigations, which created huge extra costs for mission.

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Thank you!

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