Landscape and Important Challenges

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FDA Development of New Tuberculosis Treatment Regimens
July 19, 2017

Outline

- TB Burden: United States and Global
- Current Treatment Regimens
- Challenges

Abbreviations

- H = isoniazid
- R = rifampin
- P = rifapentine
- E = ethambutol
- Z = pyrazinamide
- FQN = fluoroquinolone
- MDR = resistance to H + R
- XDR = MDR plus resistance to FQN + injectable
- LTBI = latent tuberculosis infection

TB Burden

	United States	World
New Cases of TB Disease	9,287 (2016)	10.4 million (2015)
Case Rate (per 100,000)	2.9 (2016)	142 (2015)
MDR TB Cases	89 (2015)	480,000 (2015)
XDR TB Cases	1 (2015)	45,000 (2015)
HIV-infected	539 (2016)	1.2 million (2015)
Deaths	493 (2014)	1.8 million (2015)
Estimated Prevalence of LTBI	Up to 13 million (2012)	1.7 billion (2014)

60% of TB cases worldwide occurred in just SIX COUNTRIES

58% of TB cases in the United States occurred in just SIX STATES

Current Treatment Regimens: Drug-susceptible TB

	United States (CDC)	World Health Organization
Intensive Phase	HRZE 2 months	HRZE 2 months
Continuation Phase	HR 4 months	HR 4 months
Dosing	Daily Preferred	Daily
Directly Observed Therapy	Recommended	May Be Offered

Current Treatment Regimens: MDR TB

	United States (CDC)	World Health Organization
Drug Regimen	4-6 effective TB medicines based on drug-susceptibility testing	At least five effective TB medicines during the intensive phase (8 months)
Conventional Duration	18-24 months	20 months is suggested for most patients
Shorter Duration (not previously treated with second-line drugs; resistance to fluoroquinolones and second-line injectable agents excluded or considered highly unlikely)	Not recommended	9-12 months may be used instead of a conventional regimen

Current Treatment Regimens LTBI

Drug Regimen	United States (CDC)	World Health Organization
H	6-9 months daily	6-9 months daily
HP	12 weekly doses	12 weekly doses
R	4 months daily	3-4 months daily
HR	Not recommended	3-4 months daily

Challenges of Current Treatment

- Duration – already covered
- Cost
- Toxicity
- Drug-drug interactions
- Adherence
- Outcomes (drug-resistant TB)

Interrelationships

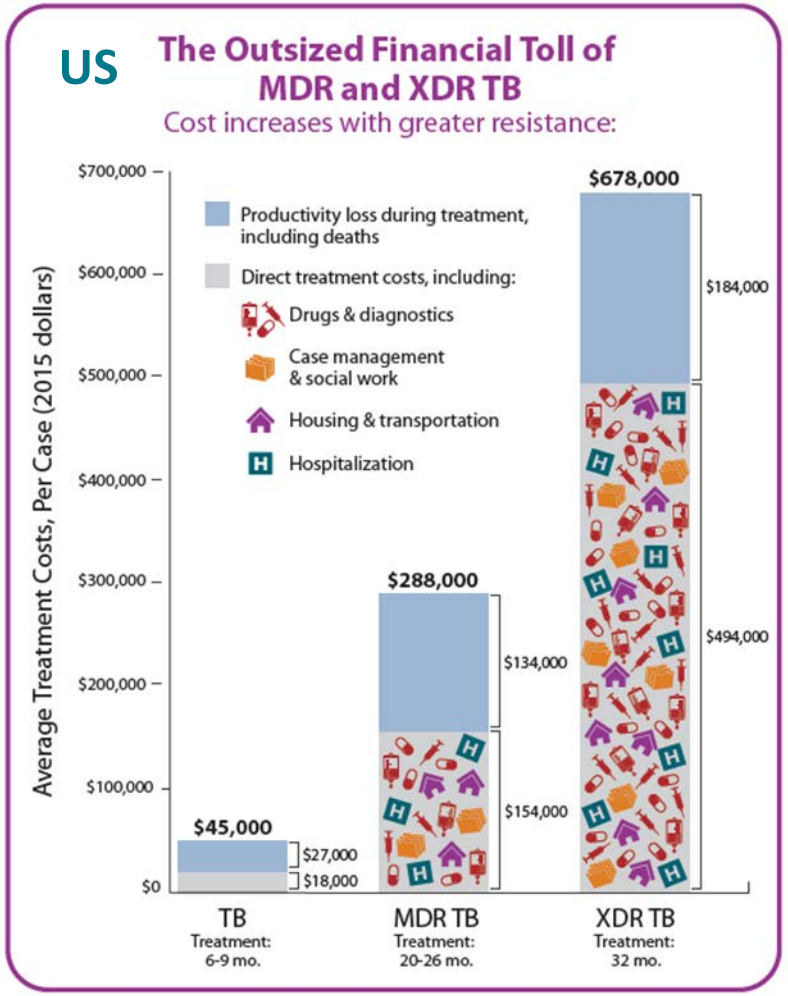
- ↑ duration → ↑cost and ↓adherence and ↑risk of toxicity
- ↑ toxicity → ↑cost and ↓adherence
- ↑ cost → ↓adherence
- ↓adherence → ↓outcomes
- ↑ toxicity → ↓outcomes

Global TB Treatment Direct Costs	
Drug-susceptible TB	$100-1,000
MDR TB	$2,000-20,000

United States Total Costs of TB Treatment

$500
TO TREAT LATENT TB INFECTION

$18,000
TO TREAT TB DISEASE



Costs of Drugs

	United States	Global Drug Facility
Drug-susceptible TB	$400	$40
MDR TB conventional	$58,000	$2,000-5,000
MDR TB short	N/A	$1,000
XDR TB	$164,000	?

Toxicity

Drug-susceptible TB regimens	Hepatotoxicity
Drug-resistant TB regimens	Hepatotoxicity Renal toxicity Ototoxicity Psychosis Thyroid dysfunction Neurotoxicity Tendinopathy Hematologic toxicity QT prolongation
LTBI regimens	Hepatotoxicity Hypersensitivity

Drug-drug interactions

INH DRUG INTERACTIONS	
Hypoglycemics	Monitor glucose, may cause hyerglycemia
Tylenol	↑hepatotoxicity
Anticoagulants	↑anticoagulant effect
Valium (&others)	↑valium toxicity
Carbamazepines	↑toxicity of both
Disulfiram (Antabuse)	Psychotic episodes
Haldol	↑haldol toxicity
Ketoconazole	↓ketoconazole effect
Dilantin	↑dilantin toxicity
Theophyllin	↑theophyllin toxicity
Valproate	↑hepatic and CNS toxicity

RIFAMPIN DRUG INTERACTIONS			
Anticoagulants	↓anticoagulants	Diltiazem	↓ diltiazem effect
Antidepressants	↓effect	Fluconazle	↓ fluconazole effect
Beta-Blockers	↓beta blockade	Itraconazole	↓ itraconazole effect
Contraceptives	↓contraceptive effect	Haloperidol	↓ haloperidal effect
Corticosteroids	Marked ↓ steroid effect	Methadone	↓ methadone effect
Cyclosporine	↓cyclosporine effect, ↑Rifampin	Dilantin	↓dilantin effect
Protease Inhibitors	Marked ↓ activity of PI, ↑Rifampin	Verapamil	↓ verapamil effect
Delavirdine	Marked ↓ delavirdine effect	Tetracyclines	↓ tetracycline effect
Efavirenz	Slight ↓ efavirenz effect, ↓ Rifampin	Trimethoprim-sulfamethoxazole	Possible Rifampin toxicity
Digoxin	↓ digoxin effect	Chloramphenicol	↓ chloramphenicol effect

Adherence

- Directly observed therapy (DOT)
  - Practice of observing the patient swallow their antituberculosis medications
  - Resource intensive = costly
    - Use of technology video/eDOT to decrease cost
- Patient-centered care
  - Incentives: interventions to motivate the patient, tailored to individual patient wishes and needs and, thus, meaningful to the patient
    - e.g., gift cards, food vouchers
  - Enablers: interventions to assist the patient in completing therapy
    - e.g., free transportation to clinic, convenient clinic hours

Outcomes

LTBI Treatment	Drug-susceptible TB	MDR TB
90% efficacy	Clinical trials: 95% cure	US programmatic: setting: 80-90% success
Completion Short-course (e.g., 3HP): 80% Long-course (e.g., 9H): 50%	Programmatic setting: 85-90% success (cure or completion)	Global programmatic setting: 50% success

Initial Targets for Improvement: Focus on Duration

- Decrease duration of drug-susceptible TB treatment to 4 months (e.g., CDC TBTC Study 31)
- Decrease duration of LTBI treatment to 4-6 weeks (e.g., CDC TBTC Study 37)
- Decrease duration of MDR TB treatment to 6-9 months (being addressed in ongoing trials)
  - Trials also looking for improved outcomes (85-90% success) compared with global programmatic average of 50% success

Thank You

For more information, contact CDC
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