Therapeutic threshold for rifampicin-resistant tuberculosis: a case report from Maputo, Mozambique

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Abstract

Objectives Frequently used rapid rifampicin drug susceptibility tests (RMP-DST) miss certain rifampicin resistance (RR)-conferring mutations, leaving RR-tuberculosis undetected. Unknown for RR-TB is the therapeutic threshold, the probability of disease at which there is equipoise between treating and not treating. In Mozambique, in a patient not responding to first-line treatment, clinicians decided to start RR-TB treatment without bacteriological proof of RR-TB. We determined the probability of RR-TB in this patient. Methods We converted probabilities and odds ratios of clinical arguments for RR-TB from literature to likelihood ratios. We then combined the associated confirming and excluding power of those arguments to estimate the probability of RR-TB when the patient was started on RR-TB treatment, and simulated its variation. We used a log-odds scale to illustrate the effect of confirming and excluding arguments. Results The starting point was the prevalence of RR-TB in Mozambique. Positive HIV-status, treatment failure after a first treatment and after retreatment were included as confirming arguments, and RMP-DST showing rifampicin susceptibility as excluding argument for RR-TB. In this patient, the probability of RR-TB was 46.6% (95% uncertainty interval: 25.0%-72.0%) when RR-TB treatment was started. Treatment failure and retreatment failure provided strong confirming arguments, and the RMP-DST result a strong excluding argument for RR-TB. Conclusions The therapeutic threshold to start RR-TB-treatment is unknown but probably lower than 47%. The uncertainty in our estimation reflects the clinical uncertainty in low-resource settings. Determining the RR-TB therapeutic threshold is needed to guide clinical decisions.

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Treatment history in another treatment centre
Drug included in the regimen, DST unknown
R DST shows resistance (mutation)
S DST shows susceptibility

Year	2014 - 2018	2018								2019										
Month on treatment		M0'	M1'	M0	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16
	2014- April 2018	May	June	July	Aug	Sept	Oct	Nov	Dec	Jan	Feb	March	April	May	June	July	Aug	Sept	Oct	Nov
Tuberculosis treatment																				
Rifampicin		S	S																	
Isoniazid			R (KatG, inhA)																	
Ethambutol		STOP																		
Pyrazinamid		STOP													STOP					
Streptomycin																				
Levofloxacin		STOP	R (GyrA)																	
Capreomycin		STOP	S																	
Ethionamid		STOP	R																	
Cycloserin		STOP																		
Bedaquiline																				
Delamanid																				
Clofazimin																				
Linezolid										STOP										
Para aminosalicylic acid				STOP																
Anti-retroviral treatment																				
EFV-3TC-TDF																				
RAL-3TC-TDF																				
Laboratory results																				
Sputum microscopy		+++	++	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N
Culture				C	C				N		N	N	N	N	C	N	N	N	N	pending
CD4			139							332										
Viral Load			23345					<1000										<1000		
White blood cell count			11.5			10.4			8.8			7.3			6.7	6.5		6.5		
Platelets count			622			664			513			246			329	339		419		
Hemoglobin			11.8			12.6			13			12.6			13	13.1		13.3		
Creatinin			40			44						58				64		82		
Creatinin Clearance			116			123						96				87		73		
GOT			33			43						102			122	77		51		
GPT			18			20						132			111	99		91		
QTcF			360			380									400	420		380		
Audiometry			normal			normal						normal				normal			normal	
Body-mass index			17.5		17.9	18.3		18.6		18.9	19.1									
Adverse event (grade)																				
Gastro-intestinal toxicity		nausea, vomiting			abdominal pain															
Paresthesia					2		2	2	2	3										
Hepatotoxicity															3