Clinical pharmacy in the era of an injection-free regimen for drug-resistant tuberculosis

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Background

Tuberculosis (TB) is the ninth leading cause of death worldwide with the 2019 global report placing South Africa (SA) among the six high TB burden countries.[1] Globally, treatment success rates (cured and completed treatment) for multidrug resistant tuberculosis (MDR-TB) in the 2016 cohort were 56% and for extensively drug-resistant TB (XDR-TB) 39%. Despite major investments in medicine, diagnostics and programmatic management, low treatment success rates, high failure and loss to follow up rates have been reported for DR-TB globally and in SA.

Historically, treatment for DR-TB has been long (18–24 months), with an injection given for 6–9 months, in combination with oral medicine selected from the World Health Organization's (WHO) group 1–5 list of DR-TB medicines.[2-5] The past five years have seen revolutionary changes in the diagnosis and management of rifampicin resistant (RR-TB), including the use of new and repurposed drugs and novel therapeutic approaches.[3] In 2018, for the first time ever, the WHO recommended the use of all-oral regimens for the treatment of RR-TB and issued guidance supporting the use of short-course, all-oral regimens under closely monitored conditions.[4] South Africa, a global leader in introducing innovation to the field of RR-TB, adopted the new WHO guidelines.[5]

In 2014, the World Health Assembly unanimously approved the End TB Strategy, a 20-year strategy to "end the global TB epidemic", with the vision of a world with "zero deaths, disease and suffering due to TB".[6] The Global Plan introduces three people-centred targets called the 90-(90)-90 targets: to reach 90% of all people who need TB treatment, including 90% of people in key populations, and achieve at least 90% treatment success. The adoption of the injection-free, short-course treatment regimen, utilising new and repurposed medicine, is an attempt to reach these targets and calls for an interdisciplinary approach with the patient at the centre.

Pharmacists are well-placed as leaders in turning the tide against this deadly yet curable disease, as part of an interdisciplinary team. Optimal use of pharmacists' competencies, training and skills will allow them to contribute to these priorities. Barriers to pharmacists implementing their scope of practice fully have been identified, particularly in the public sector, such as staff shortages, high patient workload and lack of access to information.

Clinical pharmacists play a major role in all healthcare settings and are a primary source of information and advice regarding the safe, appropriate, and cost-effective use of medicines. Clinical pharmacists assume responsibility and accountability for managing medication therapy in direct patient care settings, in collaboration with other healthcare professionals, and generate, disseminate, and apply new knowledge that contributes to improved health and quality of life.[7] Many studies have shown that clinical pharmacists can effectively identify and prevent clinically significant drug-related problems, and that physicians acknowledge and act on clinical pharmacists' suggestions for interventions to identified drug-related problems.[8] Although the category of clinical pharmacist has not yet been finalised in the public service, pharmacists possess in-depth knowledge of medicines and a foundational understanding of the biomedical, pharmaceutical, socio-behavioural, and clinical sciences necessary to embrace this role. The current DR-TB environment dictates that all pharmacists expand their scope of practice in order to ensure the safe and effective use of medicine.

This scenario presentation described the development of an integrated TB/HIV prescription booklet, which enabled pharmacists to improve their role in the management of patients diagnosed with DR-TB.

Methods

Pharmacists led discussions in the interdisciplinary team at the Centralized Drug Resistant Tuberculosis Unit, King Dinuzulu Hospital, on the safe and appropriate use of new and repurposed medicines. Gaps were identified in processes at facility level, specifically the lack of access to information for pharmacists to monitor and intervene in clinical management. An integrated prescription book that enabled prescribing for TB, HIV and comorbidities in a single prescription, with fields that enabled good clinical management practices, was developed. The prescription was piloted and ease of use was assessed.

Results

An integrated prescription book was developed, which required the prescriber to use a single form to prescribe all medicines for a patient,

Figure 1: Prescription booklet elements, showing the cover sheet, day 1-14 TB and ARV sheets, discharge and out-patient sheets

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Prescription for Integration of Drug Resistant Tuberculosis, HIV

And Non-Communicable Diseases Management

Initiating Hospital								
Hospital Practice Number								
DR TB REGIMEN	**Short**		**Long**		**Long individualized for FLQ/XDR**		**Other**	
START / CHANGE DATE								

Patient Sticker

Patient Name		**Date of Birth** (dd/mm/yyyy)	
Patient Identity Number		**Age (years)**	
Gender		**Allergies**	
Patient Address			
Patient Contact Number			
Patient Hospital Number			
Treatment Supporter Contact Number			
Patient TB Numbers (Previous and Current)	1.	2.	3.
Treatment Start Date (current episode)			
Clofazimine (C) Approval Number			
Delaminid (DL) Approval Number			
Delaminid (DLM)Treatment	**Start**	**Stop**	
Bedaquiline start date		**Bedaquiline end date**	
Bedaquiline extension date		**DLM extension date**	

DAY 1-14 TB PRESCRIPTION (TO BE USED FOR INPATIENTS AND OUTPATIENTS)

Date		Weight		Review Date	
Outpatient		Inpatient		Ward	
Prescriber		Signature		Qualification	

Short		**Long**		**FLQ/XDR**	
HIV Status (tick)	Neg	Pos	On ART		
Regimen			ARV Switch Required		
Baseline CrCl:		Hb:		QTcF	

Section A : DR TB Prescription							**Section B: Administration Record For In Patients**													
Medicine	**Dose**	**Freq.**	**Duration**	**Qty.**	**Signature of dispenser**	**Date**	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
							Date →														
							Time ↓														
Pyrazinamide		Daily po	14 days																		
Ethambutol		Daily po	14 days																		
Levofloxacin		Daily po	14 days																		
Clofazimine	100mg	Daily po	14 days																		
Linezolid	600mg	Daily po	14 days																		
Bedaquiline	400mg	Daily po	14 days																		
Isoniazid		Daily po	14 days																		
Terizidone		Daily po	14 days																		
Para-amino salicylic acid		Daily po	14 days																		
Delaminid		Twice Daily po	14 days																		
Ethionamide		Daily po	14 days																		
Imipenem / Cilastatin		Twice daily IVI	14 days																		
Amoxillin Clavulanic acid		Twice daily po	14 days																		
Amikacin		Daily IMI	14 days																		
Pyridoxine		Daily po	14 days																		
Moxifloxacin	400mg	Daily po	14 days																		

DAY 1-14 ARV PRESCRIPTION

Date		Ward		Prescriber		Signature		Qualifications	
Review Date		Weight							
CD4		VIRAL LOAD							

Section B : ART Prescription							Section B: Administration Record For In Patients													
Medicine	**Dose**	**Freq.**	**Duration**	**Qty.**	**Signature of dispenser**	**Date**	Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
							Date														
							Time														
TDF/FTC/EFV		D po	1/12																		
Nevirapine (NVP)		D po	1/12																		
Tenofovir (TDF)		D po	1/12																		
Abacavir (ABC)		D po	1/12																		
Zidovudine (AZT)		D po	1/12																		
Lamivudine (3TC)		po	1/12																		
TDF/3TC/DLT		po	1/12																		
Dolutegravir (DLT)		Po	1/12																		
TDF/FTC		Po	1/12																		
Lopinovir / R		po	1/12																		
Tenofovir/ Dolutegravir /Lamivudine / (TLD)		po	1/12																		

Additional Acute Medication			Comments

PASS OUT/ TTO TB PRESCRIPTION

TTO – do not use as a monthly outpatient Rx.				Month			Month			Month			Month			Month			Month		
				Discharge Date			Discharge Date			Discharge Date			Discharge Date			Discharge Date			Discharge Date		
				Return Date			Return Date			Return Date			Return Date			Return Date			Return Date		
				Weight			Weight			Weight			Weight			Weight			Weight		
				CrCl			CrCl			CrCl			CrCl			CrCl			CrCl		
Medicine	Dose	Freq.	Dur	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date
Pyrazinamide		D po																			
Ethambutol		D po																			
Levofloxacin		D po																			
Clofazimine	100	D po																			
Linezolid	600	D po																			
Bedaquiline	200	3 x /week po																			
Isoniazid		D po																			
Terizidone		D po																			
Para-amino salicylic acid		D po																			
Delaminid		Twice daily po																			
Ethionamide		D po																			
Imipenem / Cilastatin		Twice daily ivi																			
Amoxillin Clavulanic acid		Twice daily po																			
Amikacin		D imi																			
Pyridoxine		D po																			
Moxifloxacin	400	D po																			
Prescriber																					
Signature																					
Qualification																					

OUTPATIENT TB PRESCRIPTION

HIV Status	Pos		Neg		ARV Regimen			SHORT		LONG		INDIVIDUALIZED								
CrCl:					Month			Month		Month		Month		Month		Month		Month		
					Date			Date		Date		Date		Date		Date		Date		
					Weight			Weight		Weight		Weight		Weight		Weight		Weight		
					QTcF			QTcF		QTcF		QTcF		QTcF		QTcF		QTcF		
Medicine	Dose	Freq.		Dur	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date
Pyrazinamide		D po																				
Ethambutol		D po																				
Levofloxacin		D po																				
Clofazimine	100	D po																				
Linezolid	600	D po																				
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Amoxillin Clavulanic acid		Twice daily po																				
Amikacin		D imi																				
Pyridoxine		D po																				
Moxifloxacin	400	D po																				
Prescriber																						
Signature																						
Qualifications																						

OUTPATIENT ARV PRESCRIPTION

				Month			Month			Month			Month			Month			Month		
				Date			Date			Date			Date			Date			Date		
				Weight			Weight			Weight			Weight			Weight			Weight		
				CD4			CD4			CD4			CD4			CD4			CD4		
				Viral load			Viral load			Viral load			Viral load			Viral load			Viral load		
Medicine	Dose	Freq.	Duration	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date	QTY	Sign	Date
TDF/FTC/EFV		D po	1/12																		
Nevirapine (NVP)		D po	1/12																		
Tenofovir (TDF)		D po	1/12																		
Abacavir (ABC)		D po	1/12																		
Zidovudine (AZT)		D po	1/12																		
Lamivudine (3TC)		po	1/12																		
TDF/3TC/DLT		po	1/12																		
Dolutegravir (DLT)		Po	1/12																		
TDF/FTC		Po	1/12																		
Lopinovir / R		po	1/12																		
Tenofovir/Dolutegravir /Lamivudine / (TLD)		po	1/12																		
Prescriber																					
Signature																					
Qualifications																					

Additional Acute Medication		Comments

enabling assessment of drug-drug interactions and coordinated dispensing and clinical pharmacy interventions. The integrated prescription booklet was pre-printed with all the DR-TB medicine and antiretrovirals, recommended doses, and frequency in an easy to use format. Prescribers could select the medicine in tick boxes based on weight and complete a minimum of fields in order to comply with the legal requirements for a prescription. The prescription also accommodated inpatient care, with space to document administration of medicines by nurses, as well as discharge and outpatient prescriptions. The prescription included fields to enter HIV status, CD4 count, viral load, creatinine clearance, body mass and cardiac (QTCf) results. The prescription booklet included guidance notes on the new WHO classification as well as common and overlapping side effects of DR-TB medicine and antiretrovirals (ARVS), so it served as a comprehensive resource for both prescribers and pharmacists. The prescription booklet was piloted and input obtained from end users. Changes were made to the layout, font, spacing and sequence of medicine for ease of use. An end user acceptability questionnaire was completed at the end of the pilot. The final layout is shown in Figure 1.

Discussion

Pharmacists must work as part of the interdisciplinary team to ensure that patients diagnosed with DR-TB receive the correct regimen at the correct dose based on the resistance patterns with no drug-drug interactions and active drug safety monitoring throughout the continuum of care. South Africa initially introduced bedaquiline, one of two new agents to treat DR-TB, into the treatment guidelines under a clinical access programme (BCAP) followed by rapid registration in 2015.[5] The rapid adoption of WHO guidelines resulted in the use of unregistered medicines, such as clofazimine, and repurposed medicines with poorly documented or no safety and efficacy data in the South African population. This required pharmacists to expand their clinical role in order to ensure the safety and efficacy of the new agents. Pharmacists at King Dinuzulu Hospital actively participated in training the multidisciplinary team on side effects related to DR-TB medicine, active drug safety monitoring and drug-drug interactions in close collaboration with clinicians and nurses. Pharmacists played a major role in clinical audits of medicines use at newly activated initiating sites as part of the multidisciplinary team. The audit focused on medicine selection, dose and duration, documenting and managing side effects as well as treatment outcomes. Access to patient information, medication history and laboratory results were essential for the pharmacist to be able to perform their clinical duties.

Standardised stationery, in the form of patient clinical folders, patient carrier cards and manual DR-TB registers, is a key component of the programmatic management of DR-TB. The current clinical folder contains fields that must be completed by the nurse, clinician, social worker and audiologist and provides a complete clinical history of the patient. However, no prescription is included. Medicines were therefore prescribed in different formats depending on the model of care and facility. Separate inpatient, outpatient and discharge prescriptions were used, with ARVs prescribed separately. This resulted in a fragmented medicine history with loose pages and missing information. A facility-specific barrier to clinical pharmacy was that the clinical folder was not sent to pharmacy due to the risk of misplaced files. As a result, drug-drug interactions were missed, duration of treatment might be sub-optimal, and poor patient outcomes were likely.

The pre-printed prescription book developed at King Dinuzulu Hospital provides an integrated record of patients' treatment history. It allows the multidisciplinary team to collaborate on the patients' medication history and improves patient management and medicine safety. The prescription book is now used at all facilities in eThekwini and is being adopted at many sites in KwaZulu-Natal.

Conclusion

The pre-printed integrated prescription book is an innovative tool that improves the clinical role of the pharmacist. The adoption of the injection free regimen with new and repurposed medicine has set the scene for improving the pharmaceutical value chain.

Extracts and examples from the prescription booklet can be obtained from the author on request.

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