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Strengthening the Delivery and Improving Outcomes of Drug-Resistant TB Treatment through Rational Medication Use Review

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Abstract

Introduction: A Rational Medication Use Review was conducted in health facilities in five high burden provinces (KwaZulu Natal, Western Cape, Eastern Cape, Gauteng and North West) that account for 77% of MDR-TB cases and 92% of XDR-TB in South Africa.

Methodology: A purposive sampling of health facilities was done and stratified to represent different models of DR-TB service providers including centralized sites, decentralized sites, and satellite sites. Records for review were selected randomly among patients who initiated treatment between October 2011 and December 2012 and descriptive analysis conducted.

Results: The review involved 139 patients (76.3% MDR-TB and 17.3% XDR-TB). 76.3% of them had a pre-treatment DST and this was used for regimen selection. Renal function monitoring for dose adjustment was poor although baseline serum creatinine values were available on record for 69.1% of the patients. There was a high degree of missed doses with 66.7% of the patients having at least one missed dose. Co-morbid conditions were common with 66.2%, 13.0% and 5.8% of the patents with HIV, hypertension and seizure disorders respectively. Only 30.2% of the MDR-TB patents and 50% of the XDR-TB patients had been assessed for adverse drug reactions during the intensive phase although 125 episodes of ADRs were on record. Serum creatinine monitoring was not consistent (only 22.3% of patients had monthly values) although 16.1% of the patients had levels that would have required dose adjustments that were not done.

Conclusion: There are many factors related to the patient, drug therapy, health care providers, and the health system that may adversely influence DR-TB treatment outcomes and patient safety. These can be detected early through regular rational medication use review and institutionalization of the process. This however requires a multidisciplinary approach with involvement of levels of the health system and various institutions involved TB in medication use.

Keywords: Tuberculosis; Drug resistance; Pharmacotherapy

Introduction

There were 580,000 newly reported cases of multidrug and rifampicin resistant tuberculosis (MDR/RR-TB) globally in 2015 [1] with an estimated 9% of these as extensively drug resistant tuberculosis (XDR-TB) [2]. During the same period, an estimated 75% of TB-related deaths occurred among patients co-infected with HIV. Global drug-resistant tuberculosis (DR-TB) treatment outcome data for 2013 and 2014 cohorts showed an overall treatment success rate of 52% for MDR-TB (2013 cohort) and 28% for XDR-TB 2013 respectively [1]. Studies in some countries have identified retreatment, alcohol abuse, age, socioeconomic status, and immigrant status as determinants of development of MDR-TB [3-6]. There have been intensified efforts towards development of new, effective, and less toxic medicines particularly against XDR-TB.

Definitions of Drug-Resistant Tb and Patient Classification

Cases of drug-resistant (DR) TB are classified according to the resistance patterns as demonstrated by drug susceptibility testing (DST). Depending on the drug or class of drugs that record resistance, the Mycobacteria may be classified as mono-, poly-, multi-, or extensively drug resistant. Rifampicin is considered a cornerstone of TB treatment, is therefore specifically reported as rifampicin-resistant (RR) TB.

Patients with DR-TB are classified in several categories based on their disease and treatment history. There are five possible categories: new, relapse, treatment after loss to follow-up, treatment after failure of first treatment, and treatment after failure of re-treatment.

In South Africa, estimates in a 2014 survey indicated that MDR/RR-TB comprised 3.5% of new TB cases and 7.1% of previously treated cases. Outcome data for 2013 showed a 48% and 24% treatment success rates for MDR/RR and XDR-TB respectively [1]. The epidemiological picture in South Africa varies greatly with some provinces reporting significantly higher burdens of disease.

South Africa is currently implementing decentralization and deinstitutionalization of MDR- and RR-TB treatment aimed at providing effective treatment for all patients while recognizing the social and family responsibilities. This strategy was expected to result in prompt diagnosis and early initiation of therapy, reduced hospital stays, increased treatment coverage, improved treatment success rate, increased social acceptability of treatment, and enhanced capacity of provincial health systems including primary health care (PHC) settings to manage DR-TB.

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Guidelines for management of Dr-Tb in South Africa

Management of TB in South Africa is guided by the 'National Tuberculosis Management Guidelines (2014)', the 'South African Antiretroviral Treatment Guidelines (2015)', 'Management of Drug-Resistant Tuberculosis: Policy Guidelines (Updated-January 2013)' and the 'Policy Framework On Decentralized And Deinstitutionalized Management of MDR-TB for South Africa' that specifically provide guidance on the management of DR-TB and the decentralization and de-institutionalization of management of DR-TB.

These guidelines provide programme managers and health providers with information on the overall process involved in TB case-finding, diagnosis, treatment and monitoring to enable prompt detection and diagnosis, maximize uptake and acceptance of treatment, improve cure rates, and ultimately reduce transmission and development of drug resistance.

Drug-resistant Tb pharmacotherapy

According to the Policy Guidelines for the management of DR-TB in South Africa [7], all newly diagnosed MDR-TB patients receive a standardized regimen based on data from Drug Resistance Surveys (DRS). These regimens are based on drugs classified as second line. The therapy may be individualized later as the results of DST become available. In patients who are clinically diagnosed, particularly those exposed through known MDR-TB patients, empiric treatment based on DRS and primary contact DST is used and consequently therapy is individualized based on the results of the patient-specific DST.

In South Africa, the recommended duration of MDR-TB treatment is at least 6 months for the injectable phase with the continuation phase lasting for 18 months after culture conversion. The same criteria apply for XDR-TB, but clinical assessment of individual patients is also required to decide on the completion of treatment. Patients previously exposed to second-line TB drugs require an individualized regimen [7].

Challenges of Dr-Tb pharmacotherapy

The treatment of DR-TB faces several challenges in implementation. These include:

- **Limited options and costs of drugs:** The management of DR-TB requires the use of a combination of newer and usually more expensive drugs that are taken for a much longer duration as compared to drug sensitive (DS) TB [8].
- **Strong association of TB and HIV:** The presence of HIV makes a person more vulnerable to developing TB disease and having TB disease accelerates HIV disease progression [9]. The concurrent TB/HIV treatment in co-infected patients increases the risk of toxicity drugs used to treat these diseases are known to have overlapping toxicity profiles [10].
- **Side effects and toxicity:** The combination therapy for DR-TB presents potential drug-drug interactions and enhanced drug related toxicity (nausea and vomiting, life-threatening liver and renal toxicity etc.) [11] that potentially affect the willingness of the patient to take the required medication and complete the prescribed drug regimen [12,13]. The common concurrent use of traditional and herbal medicines for TB treatment exposes the patient to potential treatment failure or increased toxicity as a result of pharmacodynamic and pharmacokinetic interactions [14,15].
- **Adherence challenges:** Factors that affect adherence include economic and structural factors, patient-related factors, regimen complexity, supportive relationships between the health provider and the patient, and pattern of health care delivery [16]. Additionally, patients on XDR-TB treatment stop treatment early due to treatment fatigue, when they are feeling better, or when they do not sputum-convert and they believe continuing treatment is futile [17].
- **Individualized therapy and treatment monitoring:** Due to different resistance patterns and co-morbidities, drug interactions and physiological changes in DR-TB patients, the selection of drugs is individualized. This requires highly trained clinicians to initiate treatment and increases the chances of medication errors as a result of wrong drug and/or dose selection.

Rational medication use review

Rational use of medication is a critical component of the management of TB. As the epidemic progresses and resistance to available medicines increases, newer drugs are being researched, developed, and used particularly for DR-TB. These newer drugs are usually more toxic and require longer treatment periods to achieve complete cure, further complicating treatment interventions.

With this scenario, regular review of medication use in terms of rationality and the detection and management of potential side effects that may influence treatment completion and success is paramount.

Rational Medication Use Review (RMUR) is a planned, criteria-based systematic process for monitoring, evaluating, and continually improving medication use, with the aim of improving medication-related outcomes for a group of patients [18,8]. This quality improvement process has application in all settings where pharmacologically active substances are used. It focuses on assessing and improving one or more of the steps involved in medication use (patient assessment, prescribing, preparation and dispensing, administration, patient monitoring for adherence, medication safety and efficacy, and patient education).

Methodology

Survey design

This evaluation utilized a cross-sectional, descriptive, and multiple-site evaluation design involving a combination of methods including desk review and individual patient data abstraction. The aim was to determine the level of compliance by the health workers to guidelines for the management of MDR- and XDR-TB in South Africa. The criteria for the RMUR were developed to measure the appropriateness, timeliness, safety, continuity, efficiency, and effectiveness of the MDR-TB management process. These criteria described the various indicators and expected threshold across the whole medication use process. The various considerations were related to diagnosis, pre-treatment assessment, treatment initiation, regimen selection and dosing.

A purposive sample of five high-burden provinces (KwaZulu-Natal, Western Cape, Eastern Cape, Gauteng, and North West) was conducted. These provinces account for 77% of MDR-TB cases and 92% of XDR-TB cases in South Africa. The sampling of the facilities was stratified to represent the different models of DR-TB service providers including centralized sites, decentralized sites, and satellite sites. Records were selected for review for patients who were initiated on treatment during the period between October 2011 and December 2012. Ethical approval was not necessary since the RMUR is a quality assurance and improvement process and was undertaken as part of a wider programme evaluation process led by the National Department of Health (NDOH) and the World Health Organization (WHO).

Data collection and analysis

A Data Extraction Tool was developed based on the agreed RMUR criteria with an accompanying Data Extraction Guide. The developed tool and criteria were shared with NDOH and WHO for input and revised accordingly. Through the NDOH, healthcare providers in the selected facilities were identified and briefed on the data collection process and undertook the data collection exercise. Data was captured on Excel® spread sheets and descriptive analysis conducted.

Results

The review included 139 patients aged between 6 months and 84 years. There were 10 patients under 8 years and most of the patients (32.4%) reviewed were between 26 and 35 years old. Of the patients' files reviewed, 63 (45.3%) were male and 72 (51.8%) were female. The gender of four patients could not be established from the records.

HIV status and patient classification

Most of the patients were HIV positive (61.2%) and had been diagnosed with HIV prior to TB diagnosis (58.3%). All the HIV positive patients were on antiretroviral therapy (ART) indicating good compliance with guidelines recommending the initiation of ART in all patients with TB.

Patient categorization

Most of the patients (39.6%) were classified as new patients and had not received treatment for TB previously. This indicated a high incidence of DR-TB community transmission. A smaller proportion (20.1%) of the reviewed patients were receiving treatment after loss to follow up and 15.8% after failure of first treatment.

Laboratory testing

About three quarters (76.3%) of the participants underwent DST, 73.4% bacterial culture, and 67.6% sputum microscopy. Most (76.3%) had MDR-TB and 17.3% were reported with XDR-TB. Most (84.9%) of the patients had pulmonary TB while 4.3% had extra-pulmonary TB. One patient had both pulmonary and extra-pulmonary TB.

Pre-treatment preparation

In most (61.9%) of the patients, details of the treatment were documented to have been communicated to the patient. However, in 38.1% of the patients, this information was not available on record indicating that either it was not communicated, or it was done but not documented. According to the patient records, only 36.7% of family members and caregivers were counselled on the implication of treatment (length of hospital stay, treatment procedures and post-treatment interventions). This is an important aspect of the treatment as they form a critical social support system for the patient particularly with the decentralized and deinstitutionalized strategy.

Regimen selection and initial dose determination

Most (84.9%) of the patients had a DST on record indicating that the test was performed and used in regimen selection. All initial dosing was done using the standardized regimens and doses proposed in the national guidelines.

Renal function and dose adjustment

Baseline Serum Creatinine results were available for 69.1% of the reviewed patients; a significantly low rate considering that it is recommended for all patients at the time of treatment initiation. Analysis of creatinine clearance (CrCl) in a cohort of 31 patients that had baseline Serum Creatinine results on record indicated that 13 (8 males and 5 female) of the patients had CrCl values below the lower limits of the values. In 5 (16.1%) of these patients, CrCl values were below 30 ml/min indicating that these cases required dose adjustment that was not undertaken. Additionally, the recommended monthly follow-up Serum Creatinine tests were not consistently done. This means that there may have been instances that dose adjustment may have been indicated as treatment progressed but were missed.

Duration of treatment

Among the MDR-TB patients, the mean duration of the intensive phase was 5.6 months and 13.2 months for the continuation phase. For XDR-TB patients, the mean duration of the intensive phase was found to be 5.5 months and 13.8 months for continuation phase.

Adherence

From the reviewed patient records, 66.7% of the patients had missed at least one dose; this was as high as 90% in some facilities. However, due to incomplete records of drug administration, it was not possible to establish the exact number of missed doses and therefore the level of adherence could not be established.

Comorbidities

There was a high prevalence of comorbidities among the reviewed patients. Most patients (66.2%) had HIV while 13.0% had hypertension and 5.8% reported seizure disorders.

Drug combinations with potential for interaction

The assessment highlighted the existence of many of the previously known and documented potential drug interactions (Table 1). In the record review, it was noted that most of the interactions were associated with ART with almost 40% reporting co-administration of fluoroquinolones with non-nucleoside reverse transcriptase inhibitors (NRTIs).

Patient review (by doctors and nurses)

In 97.8% of patient records, there were records of a doctor's review at the time of initiation of treatment. Additionally, 61 (43.9%) of the patients had been reviewed by a doctor once weekly in at least nine of the first 12 weeks. Ninety-seven (69.8%) of the patients were reviewed by a nurse for between 26-30 days during the first 30 days of treatment.

Laboratory monitoring

The treatment guidelines recommend monthly sputum microscopy and TB culture. This was assessed by determining whether these tests were done monthly during the first 12 months of treatment. Only 20.1% of the reviewed patients had monthly recommended sputum microscopy and 22.3% had TB culture tests for the 12 months respectively. Transition from the intensive to the continuation phase is guided by two consecutive culture negative tests. Most (67.0%) of the MDR-TB and 79.2% of XDR-TB patients recorded two consecutive culture negative tests to guide transition to the continuation phase of treatment.

Adverse drug reaction (ADR) monitoring

The review revealed that only 30.2% of the MDR-TB and 50.0% of XDR-TB are on record as having been assessed for side effects during the intensive phase; and 37.7% of MDR-TB and 50.0% of XDR-TB during the continuation phase respectively.

Co-morbid Condition	Anti-TB Drug	Interacting Drug	No.
HIV and AIDS	Ethionamide/Prothionamide	PIs	14
	Pyrazinamide/Ethambutol	Nevirapine	6
	PAS	Efavirenz	20
	Fluoroquinolones	All NRTIs	55
	Aminoglycosides	Tenofovir	34
	Terizidone	Efavirenz	39
Chronic obstructive pulmonary disease (COPD)	Clarithromycin	Salmeterol/ Fluticasone	2
	Clarithromycin	Dexamethasone	1
	Clarithromycin/ Levofloxacin/ Gemifloxacin/ Moxifloxacin	Formoterol/Fluticasone/ Salmeterol	3
Hypertension	Amikacin/ Kanamycin/ Streptomycin	Furosemide	3
Depression	Moxifloxacin/ Levofloxacin/ Gemifloxacin/ Clarithromycin	Fluoxetine/ Amitriptyline/ Venlafaxine	7
Diabetes	Gemifloxacin/ Levofloxacin/ Moxifloxacin	Metformin/ Sulfonylureas/Insulin	1
Psychosis/ Seizures	Clarithromycin	Phenytoin	5
	Gemifloxacin/ Moxifloxacin/ Levofloxacin/ Clarithromycin	Citalopram/Haloperidol/ Promethazine/ Risperidone	3
	Linezolid	Lithium	2
	Linezolid	Carbamazepine	1

Table 1: Recorded clinically significant potential drug interactions.

ADR profiles

A total of 125 episodes of ADRs (Figure 1) were recorded and the most common suspected ADRs included nausea and vomiting (20.8%), peripheral neuropathy (15.2%), and hearing loss (12.0%). It was not possible within the scope of this review to determine whether these ADRs were as a result of DR-TB medication or concurrently administered drugs.

Management of suspected ADRs

Most of the ADRs (54.4%) such as peripheral neuropathy, nausea and vomiting and arthralgia were managed through use of additional drugs. Hearing loss was managed mainly through dose modification and withdrawal of drug.

ADR documentation and reporting

The review revealed that most of the suspected ADRs (94.0%) were neither documented in the Adverse Drug Reaction/Product Quality Report Form nor reported to the Pharmacovigilance Centre.

Laboratory monitoring of ADR

Laboratory monitoring is a crucial component for monitoring the emergence of non-overt ADRs that may have serious implication on the health of the patient and/or in the treatment outcome. The guidelines recommend baseline and monthly monitoring of Creatinine Clearance. From the records, 94 (69.1%) of the patients had baseline CrCl but only 31 (22.3%) had monthly CrCl results on record. Of the patients who had monthly CrCl, 5 (16.1%) had levels that would have required dose adjustment but was not done.

Treatment outcomes

The treatment completion rates were higher among MDR-TB patients (56.6%) than among those with XDR-TB (37.5%). Noteworthy is the high number of patients who were lost to follow up (13.7%) and transferred out (10.1%). There were no records of outcome for those who transferred out and therefore these could not be verified.

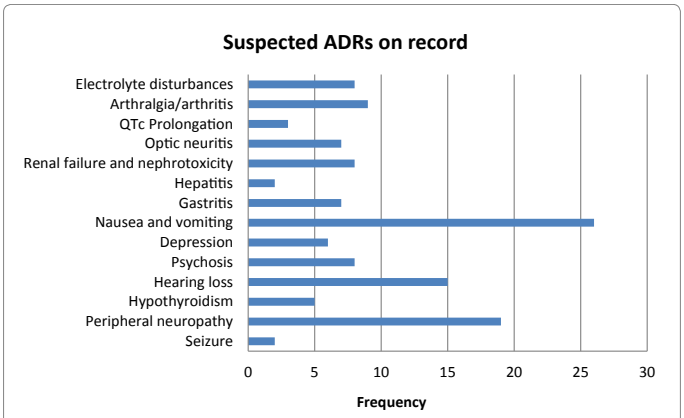

Figure 1: Relative frequencies of suspected Adverse Drug Reaction (ADR).

Discussion

Pharmacotherapy is a critical component of the management of DR-TB and it is therefore paramount that any factors that may affect optimal treatment are identified early and appropriate remedial measures taken.

Sub-optimal adherence and missed doses

Adherence to second line medications is critical for positive treatment outcomes and suboptimal adherence mediates the development and spread of drug resistance [19]. Many patients on treatment for DS-TB default on treatment and successful outcomes range from 55-95% [20]. DR-TB management is complicated by co-infection with HIV and other comorbid conditions, relatively weak health profiles of patients, high pill burden and long duration of treatment, and the poor tolerability of the medication used. Consequently, the level of adherence is lower among these patients and cure rates are significantly lower [21].

Pre-treatment adherence preparation: Adherence to both TB medications and ARVs may be affected by patient's knowledge, attitudes, and beliefs (KAB) [22]. Factors associated with KAB include poverty,

gender, education, perceived stigma around HIV or TB or both, and other social, structural, and cultural factors [23]. It is important that the patient and the family or caregivers understand the implications and value of treatment from the onset and support the initiative and thereby increasing adherence and completion of treatment. The findings from the RMUR indicate that there are limited documented efforts to promote, strengthen, and intensify pre-treatment adherence preparation that can be helpful to support treatment for outpatients and in-patients on hospital passes. This needs to be strengthened to improve adherence and retention on treatment.

Missed doses: Patients who miss doses or default on treatment have an increased risk for mortality, acquisition of additional drug-resistance, and promote continued transmission of DR-TB strains in the community [24]. This, combined with the comparatively low cure rates for DR-TB, limited drug options, and long duration of treatment, makes the implications of missed doses more critical [25].

Despite the implementation of the DOT strategy, the patient folders reviewed showed that there was a high prevalence of missed doses both in the intensive and continuation phases (as high as 90% in some health facilities). This presents a major compromise on treatment as it affects the efficacy and effectiveness of treatment leading to poor treatment outcomes and development of drug resistance. Additionally, a significant number of missed doses, especially in the intensive phase, were attributed to the outpatient model of treatment where the availability of the patient at the time of dosing could not easily be assured. There is need to intensify adherence support and monitoring in the community to ensure that the patients fully understand the implications of missed doses and have the necessary social and economic support.

Management of suspected adverse drug reactions

DR-TB is treated with a combination of drugs that are less effective but more toxic than first line drugs used in management of DS-TB [26]. Minor adverse effects are quite common and these resolve with time or can be easily managed with symptomatic treatment. However, some adverse effects can be life-threatening [27,28]. These include nephrotoxicity due to aminoglycosides, cardiotoxicity due to Fluoroquinolones, gastrointestinal toxicity due to Ethionamide or Para-aminosalicylic acid (PAS), and central nervous system toxicity due to Cycloserine [29]. Baseline evaluation assists in identifying patients who are at increased risk for adverse effects. Regular clinical and laboratory evaluation during treatment is very important in preventing adverse effects from worsening. Poor management of adverse effects increases the risk of non-adherence or irregular adherence to treatment, and may result in treatment default and treatment failure.

From the findings, it was evident that a large number of patients had documented possible side effects related to DR-TB treatment. The data however indicated low levels of active probing on side effects (up to 29.0% of patients were not regularly interviewed on side effects in the critical intensive phase). Additionally, the data indicated inconsistent use of recommended monitoring using laboratory tests (Serum Creatinine, Serum potassium, Liver function tests) to determine non-overt ADRs and facilitate pharmacotherapeutic decisions particularly in the injectable phase.

Reporting of ADRs and pharmacovigilance

Pharmacovigilance, defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem [30] is a crucial component of patient safety in DR-TB programs. The drugs used in management of DR-TB are usually newer and more toxic with little experience on long-term patient safety. This situation is worsened by the existence of many comorbid conditions (especially HIV) that are managed with drugs that also have significant patient safety concerns. It is therefore paramount that deliberate efforts are made to document these ADRs as they emerge to enable better management of DR-TB both at the individual patient and program level.

The National TB Program (NTP), together with the Medicines Control Council (MCC), has put in place mechanisms and channels for the healthcare provider to document and report ADRs to the pharmacovigilance unit [7]. This information, once analysed, assists the program to make policy decisions on the use of the drugs. Additionally, the information should be used at the health facility level to guide and improve the individual patients' treatment and ultimately improve patient safety and increase chances of cure.

From the findings of the RMUR, it emerged that there was very little documentation of the suspected ADRs in the prescribed forms (the Adverse Drug Reaction/Product Quality Report Form) and reporting to the pharmacovigilance unit. There is a need to continuously sensitize the health providers of the need and benefit of reporting the ADRs as prescribed as well as ensuring that these reports are used to enhance and improve patient care through appropriate feedback mechanisms.

Regimen and selection, and dosing adjustment

Renal insufficiency: Kidney disease is a common phenomenon in patients with DR-TB. This may be caused by renal TB disease, kidney damage due to previous injectable drug toxicity, complications of diabetes mellitus, and HIV-associated nephropathy [31]. Drugs used in the treatment of TB and associated diseases that are excreted by the kidney can be potentially toxic in patients with reduced renal function.

The national treatment guidelines recommend that patients are initiated on standardized doses of drugs selected based on results of DST. However, these standardized regimens only take into account the patient weight although renal function as well as concomitant medication needs to be considered. The guidelines recommend dose adjustments in cases of renal insufficiency mainly by recommending extension of dosing intervals while maintaining doses.

To support appropriate dose adjustment for renal insufficiency, it is recommended that CrCl be used as a guide to the need and timing of the necessary adjustments. The guidelines recommend that any patient with a CrCl below 30 ml/min should have the doses of drugs that are eliminated through the kidney adjusted. These laboratory tests are recommended at initiation of treatment and monthly during treatment especially during the intensive phase where injectable aminoglycosides are used. Without the necessary adjustment, there is a strong likelihood of high blood levels and toxicity.

The findings of the review indicated that although some patients had CrCl below the 30 ml/min threshold and a dose adjustment was necessary, they standardized doses. Other patients had values that, although they did not meet the threshold for adjustment, required very close monitoring during treatment. Unfortunately, most of the records reviewed did not have results of the recommended monthly renal function tests indicating that there was incomplete monitoring. This implies that instances where dose adjustment may have been necessary were missed.

Changes in weight: TB causes a patient to experience severe weight loss as major consequence of the disease. The situation is worse in DR-TB since the patients are very likely to have been sick for a much longer period and suffer from at least one of the common associated diseases (usually HIV). In view of this, patients showing positive progress on treatment are likely to have significant change in weight as they get better.

Dosing of MDR- and XDR-TB medicines is guided to a large extent by the patient's weight. This means that there is a strong likelihood that higher doses of the drugs may be required as treatment progresses, and the patient's condition improves (increase in weight). The health care provider should therefore be aware of the implication of weight changes and appropriately monitor it to ensure that the administered doses are ideal for the patient's weight.

Drug-drug interactions

Patients on MDR- and XDR-TB treatment are on combination regimens and this is complicated by the existence of associated diseases especially HIV. This multiple drug therapy and the drugs used in managing the comorbidities greatly increase the chances of drug interactions that may increase toxicity or reduce efficacy through pharmacokinetic and pharmacodynamic interactions.

There are many drug interactions that are associated with DR-TB treatment. Health providers should take these possible interactions into consideration while constitution treatment regimens. In many situations and considering the limited drug options available, interacting drugs may not be avoided and therefore the patient should be continuously monitored, and appropriate dose adjustments made where necessary.

The RMUR highlighted several possible interactions among patients being managed for a combination of diseases. Most interactions (85.7%) were related to antiretroviral therapy (ART); findings are consistent with the strong association between TB and HIV. These interactions need to be carefully taken into consideration since they may affect adherence (through increased toxicity) or reduce drug blood levels, and consequently compromise outcomes [32].

Treatment outcomes

Treatment of MDR-TB in programmes with largely HIV-negative patients have demonstrated treatment success rates ranging from 61-77%, and death rates between 5% and 19% [33]. The WHO Global TB report (2016) reported a 48% and 24% treatment success rate for MDR- and XDR-TB respectively in South Africa [1]. Additionally, the use of ART in co-infected patients indicated lower mortality and had a positive effect on treatment success [33].

The findings of the RMUR revealed low rates of treatment success that are comparable to available literature (36.8% for MDR and 25% for XDR). To improve outcomes, there is need to consider the high rates of loss to follow up, determine the underlying causes and intensify strategies that enhance adherence and patient retention both at the health facility and community levels.

Limitations

This rational medication use review was conducted in 2015 as part of the Evaluation of the Implementation of the Policy Framework on Decentralised and Deinstitutionalised Management of Multidrug Resistant TB in South Africa using data in patient records who were initiated on treatment for the period of October 2011 to December 2012. The authors acknowledge that due to policy amendments, some improvement may have occurred with time in the process of implementation since 2015. Additionally, some of the findings may have been as a result of poor or incomplete documentation in the patient records which was the data source.

Recommendations

RMUR is a valuable resource for health programmes to ensure and maintain high quality intervention throughout the medication use process. Although this RMUR was conducted in various provinces and facilities and general recommendations made, there is a need to institutionalize this process at the facility-level. This is because some facility-specific treatment and drug related challenges exist and these need to be identified and resolved at the facility level.

The recommendations from the RMUR are grouped by the target audience:

Patient

Adherence support and medication literacy: Several treatment challenges that may compromise adherence were identified in the study and reviewed literature. These include pill burden and fatigue and inadequate management of hospital passes. There is a need to reinforce and strengthen adherence support and medication literacy among patients to complement the DOTs strategy.

Focus on patient safety: With the more toxic drugs used in DR-TB management and the high prevalence of comorbid diseases, patient safety should be a major focus. Therefore, a safety plan that is more patient-focused should be developed and the findings used to enhance patient care and treatment benefit. Patients should therefore be encouraged to report any side effects to the nurses, doctors, and pharmacists.

Drug therapy

Treatment and pill fatigue: The long duration of treatment is a major contributor to patient attrition and loss to follow up. There is need for intensified research and development of shortened duration of therapy.

Ease of drug administration and management: Pre-packing of common drug regimens at provincial level may ease drug administration and enhance the efficiency of DOT at the peripheral level and in the community setting.

Individualized therapy: DR-TB patients present with diverse drug resistance patterns and varied metabolic/physiological profiles. In this regard, it is paramount that the system promotes individualized therapy and sound clinical judgment in some cases. This will maximize impact of treatment and increase likelihood of achieving cure.

Prevention and management of ADRS and drug interactions: There is need to focus the attention of health providers on the prevalence and implications of ADRs and potential drug interactions. This will ensure that critical parameters are well managed, and the patient achieves the maximum benefit of treatment while minimizing harm.

Health care providers

Knowledge and capacity development: Management of DR-TB is a complex intervention with continuously changing strategies and emerging new knowledge. To ensure that health workers

are kept current on best practices, there is need to formulate and intensify in-service and competency training in individualized drug dosing, prevention, and management of ADRs, Drug-Drug/Disease management and medication literacy.

Pharmacovigilance: There is a need to emphasize to healthcare workers the importance of documenting and reporting ADRs and the implications of the reports for both the program and the individual patient. Due to the high prevalence of ADRs in this population, it will be important for NDOH to prioritize training on pharmacovigilance for DR-TB.

Health system

Documentation: Tracking of progress of treatment relies on robust documentation and reporting structure. There is therefore a need to strengthen documentation and record keeping for evidence of intervention, quality assurance and continuation of care.

Treatment monitoring infrastructure and communication: Laboratory parameters are a critical component of diagnosis, drug selection and treatment monitoring. There is therefore a need to strengthen liaison between clinical and laboratory services for timely reporting of laboratory tests values especially panic values.

Institutionalize RMUR

Rational Medication Use Review (RMUR) is a valuable resource for quality assurance and programme monitoring both at the programme and facility level where medication-related challenges can be identified early and promptly managed. There is need to institutionalize regular facility-based RMUR as a tool for continuous quality improvement as well as commence medication errors monitoring.

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