Adverse effects profile of multidrug-resistant tuberculosis treatment in a South African outpatient clinic

Jacobs TQ, BSc(Hons), MBBCH, DA, MMed Student
Department of Family Medicine, University of KwaZulu-Natal
Ross A, MBChB, DCh, MFamMed, Lecturer
Department of Family Medicine, University of KwaZulu-Natal
Correspondence to: Tiras Jacobs, e-mail: tqjacobs@gmail.com
Keywords: tuberculosis, adverse effects, multidrug-resistant, HIV, HAART

Abstract

Background: Highly active antiretroviral therapy (HAART) and drugs that are used to treat multidrug-resistant tuberculosis have potentially overlapping adverse effects. Few South African studies have documented adverse effects in the multidrug-resistant tuberculosis population. This study examined the adverse effects profile in a sample of the outpatient population at the King George V Hospital Multidrug-Resistant Tuberculosis Clinic in Durban, KwaZulu-Natal.

Method: The method was an anonymous, retrospective record review of 350 patients with multidrug-resistant tuberculosis, who were attending the King George V Hospital Multidrug-Resistant Tuberculosis Clinic (2010-2011). Adverse effect profiles in patients with multidrug-resistant tuberculosis only, and those who were co-infected with the human immunodeficiency virus (HIV) who were on and not on HAART, were documented and analysed.

Results: Adverse events were recorded for 80.6% of patients. These included hearing loss (28.7%); peripheral neuropathy (23.2%); diarrhoea, nausea and vomiting (20.5%); arthralgia (15.9%); rashes and dermatological effects (excluding Stevens-Johnson syndrome) (14%); abdominal pain and dyspepsia (10.3%); and psychoses and confusion (8.3%). In this study population, 72.6% of patients were HIV positive, and 85% were concomitantly on HAART and multidrug-resistant tuberculosis treatment. Adverse events were significantly more common in patients who were HIV positive than in patients who were HIV negative with regard to peripheral neuropathy (p-value < 0.001), psychosis and confusion (p-value = 0.04), hearing loss (p-value = 0.047), and thyroid disease (p-value < 0.001). The use of HAART in patients who were HIV positive and on multidrug-resistant tuberculosis treatment was not significantly associated with the overall incidence of adverse events (p-value = 0.432). However, the calculated likelihood ratios of several individual adverse events occurring in these patients was greater. Patients who were HIV negative experienced the least adverse events.

Conclusion: The high percentage of patients in the sample population (45%) who was found to be multidrug-resistant tuberculosis positive *de novo* or while on standard tuberculosis treatment suggests that drug sensitivity testing for all patients with tuberculosis should be considered. The findings of this study support the current national policy that all patients with tuberculosis should be tested for HIV, and that all patients who are HIV positive and with multidrug-resistant tuberculosis should be on HAART. Clinicians should be supported in their function of examining, managing and recording adverse events. Reporting adverse events to the Department of Health should be encouraged. The development of a standardised recording instrument may mitigate the under-reporting of adverse events. The adverse effects profile in this study population differs from that reported in other studies.

Ⓟ Peer reviewed. (Submitted: 2011-12-12. Accepted: 2012-04-09.) © SAAFP **S Afr Fam Pract 2012;54(6):531-539**

Introduction

Tuberculosis reports that were submitted by South Africa to the World Health Organization (WHO) indicate a fivefold increase in the notification of tuberculosis over the last 20 years.[1] South Africa and Swaziland have the highest tuberculosis notification rates in the world, with an annual incidence of about 1% of their populations.[1] Despite highly effective drugs, morbidity and mortality due to *Mycobacterium tuberculosis* are increasing in South Africa, and this is fuelled by the widespread human immunodeficiency virus (HIV) epidemic.[2] Just under 2% of new patients with tuberculosis and 6.7% of retreatment patients have multidrug-resistant tuberculosis.[2] Multidrug-resistant tuberculosis is defined as *Mycobacterium* tuberculosis that is resistant to both isoniazid and rifampicin, with or without resistance to other drugs.[3] Given the number of patients with tuberculosis, this

equates to a large burden of multidrug-resistant tuberculosis in South Africa. There were 2 140 new multidrug-resistant tuberculosis cases in South Africa from 2004-2007.[4] In its policy guidelines, the Department of Health has noted that the limited number of available second-line drugs imposes limitations on the design of adequate multidrug-resistant tuberculosis treatment regimens.[2] The choice of drugs may be further restricted by adverse events that are experienced by patients.[5] Despite anecdotal reports of adverse events that relate to multidrug-resistant tuberculosis treatment, to date, only a few studies describing the extent of this problem have been undertaken in South Africa.[6] A description of the adverse events by data extraction and analysis could assist in the planning of national multidrug-resistant tuberculosis treatment strategies.

Method

Setting

The King George V Hospital Outpatient Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis Clinic in Durban was selected as the study site. This clinic serves the Ethekwini Municipality, and some surrounding districts that do not have their own multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis units. Patients with proven culture resistance to both isoniazid and rifampicin, with or without resistance to other drugs, are referred to the King George V Hospital for initiation of multidrug-resistant tuberculosis management. The standard multidrug-resistant tuberculosis regimen consists of an intensive phase of at least six months taking four oral drugs and one injectable drug, followed by a continuation phase of 18 months or less taking the four oral drugs. The King George V Hospital uses kanamycin or amikacin (injectable), ofloxacin, ethionamide, terizidone and pyrazinamide during the intensive phase. Ethambutol, a first-line drug, is also often added. Most patients who are diagnosed with multidrug-resistant tuberculosis are admitted initially, and ideally, should remain as in-patients until they are sputum-negative. However, this is not possible in all cases due to the increasing numbers of patients and limited beds. Patients are usually discharged once they are medically stable to continue treatment as outpatients. Outpatient clinics are held twice weekly. All enrolled patients are required to attend once per month. On average, between 1 400-1 800 patients are followed up at any given time, with 150-280 attending the outpatient department clinic on any given day. In consultation with a bio-statistician, a sample size of 350 was selected, which represented 25% of the study population. Inclusion criteria were all clinic attendees who had completed the first six months of treatment.

For the purposes of this study, adverse effects were defined as "any undesirable or harmful effect or effects known to be associated with or suspected to be associated with the administration of a certain drug or drugs". Many of the adverse events of standard tuberculosis treatment may also occur with multidrug-resistant tuberculosis treatment. The majority of patients included in this study had recently been on, or were still on, standard tuberculosis treatment drugs, when they were changed over to multidrug-resistant tuberculosis treatment. Therefore, it was necessary to record any adverse events at the initial presentation, prior to starting multidrug-resistant tuberculosis treatment. In addition, any adverse events that developed during the first six months of multidrug-resistant tuberculosis treatment were also analysed. Attendees with extensively drug-resistant tuberculosis, those on non-standard treatment regimens, non-compliant patients, and those who failed to attend regularly were excluded from the study. During July and August 2011, patient files were randomly selected from the record archives. Files are stored in several filing cabinets according to surname. Within each cabinet, files are randomly placed, depending on when the patient was seen in the clinic. The first 25 files in each cabinet were selected for analysis. In total, 405 files were reviewed, and 350 files met the inclusion criteria.

An anonymous, retrospective record review was performed using a data capture form. This form was derived from WHO tuberculosis monitoring and reporting guidelines,[7] and adverse events profiles reported in other studies.[8-11] The WHO designed a system to identify adverse events that could be reliably diagnosed clinically. Although some adverse events, such as depression and anxiety, are not clearly defined, this is the method that is used in tuberculosis clinics in the majority of low-income countries to monitor and report adverse events. To compare results with existing studies, the WHO monitoring tool was used. The WHO advises that routine laboratory monitoring is not necessary.[12] However, wherever available, supporting laboratory results were included.

Data were entered into SPSS® version 19.0 (SPSS, Chicago, Illinois, USA), and analysed descriptively. Frequency tables were used to summarise categorical data, while quantitative data were assessed using summary statistics, such as mean, standard deviation and range. Cross tabulations and Pearson's chi-square tests or Fisher's exact tests were used to assess associations between HIV infection and adverse effects, or the use of highly active antiretroviral therapy (HAART) and adverse effects. A p-value < 0.05 was considered to be significant.

Ethical considerations

Permission to conduct this study was granted by the King George V Hospital management and the KwaZulu-Natal

Department of Health. Final ethics approval (BE 158/010) was granted by the Post Graduate Committee and the Biomedical Research Ethics Committee at the NR Mandela Medical School in Durban.

Results

A total of 405 randomly selected patient files were reviewed, of which 350 records were eligible for inclusion in the study. Of those files that were not included in the analysis, 45 pertained to patients with extensively drug-resistant tuberculosis, and this constituted 11.1% of the total sample. The study sample comprised 182 females and 168 males, with a mean age of 35.65 years [standard deviation (SD) 11.24]. A single drug was omitted from the standard regimen in 18 (5%) patients. These patients continued to receive at least one multidrug-resistant tuberculosis drug from each drug class. In 13 cases, terizidone was omitted, but ethionamide, which is also an oral bacteriostatic agent, was continued. In five cases, ethambutol was omitted, but pyrazinamide, another first-line oral agent, was continued. As these are considered to be acceptable alternate regimens, these 18 patients were included in the study group. Of the 350 patients, the HIV status of 341 patients was documented. Of these, 254/341 (74.5%) were HIV positive, and 216/254 (85%) were concomitantly on HAART and multidrug-resistant tuberculosis treatment.

Adverse events were reported by 97 patients prior to initiating multidrug-resistant tuberculosis treatment. Of these patients, 84 were HIV positive (87%), 11 were HIV negative, and two had an unknown HIV status. Seventy-two of the 84 patients were HIV positive (76%) and on HAART, 10 patients were not on HAART (p-value < 0.001), and there was no documentation with regard to HAART for the remaining two patients who were HIV positive.

With regard to exposure to previous tuberculosis treatment, 31 patients with tuberculosis who were treatment-naïve were started on multidrug-resistant tuberculosis treatment, and not standard tuberculosis treatment, because of drug-sensitivity testing prior to treatment (primary multidrug-resistant tuberculosis treatment). Of the remaining 319 patients, 127 (40%) were on standard first-line, and 143 (45%) were on second-line, tuberculosis retreatment regimens, when they were found to have multidrug-resistant tuberculosis. (see Table I)

Table I: Diagnosis of multidrug-resistant tuberculosis in relation to the patient's tuberculosis treatment regimen at the time

Diagnosed with multidrug-resistant tuberculosis (excluding the 31 *de novo* patients with multidrug-resistant tuberculosis)	No of patients (n = 319)
While on standard first-line tuberculosis treatment	127
During first exposure to standard tuberculosis retreatment regimen with second-line drugs	143
During second exposure to standard tuberculosis retreatment regimen with second-line drugs	46
During third exposure to standard tuberculosis retreatment regimen with second-line drugs	3

Patients who were diagnosed with multidrug-resistant tuberculosis, while being exposed to standard tuberculosis treatment for the first time, were significantly more likely to be HIV positive than HIV negative (p-value = 0.005). There was a statistically significant higher incidence of multidrug-resistant tuberculosis in females compared to males, with an odds ratio of 2.49 (95% confidence interval 1.58-3.92; p-value < 0.001). Tuberculosis contact history and HIV status was significant in males (p-value = 0.027), but not in females (p-value = 0.068). Males who were HIV positive in this sub-group were more likely to have a positive tuberculosis contact history than females who were HIV positive.

Two hundred and eight-two patients (80.6%) developed one or more adverse events while on multidrug-resistant tuberculosis treatment. This group consisted of 210 (82.7%) of the patients who were HIV positive, and 67 (77%) of the patients who were HIV negative. The HIV status of the remaining five patients was unknown. These adverse events required either dose reduction, withdrawal of the suspected drug, or symptomatic treatment and monitoring. The higher incidence of adverse events in patients who were HIV positive, compared with patients who were HIV negative, was statistically significant for peripheral neuropathy (p-value < 0.001), psychosis and confusion (p-value = 0.04), hearing loss and vestibular disturbances (p-value = 0.047), and thyroid disease (p-value < 0.001).

There was no statistically significant difference in the development of adverse events between patients who were HIV positive and who were on multidrug-resistant tuberculosis treatment and HAART, and those who were not on HAART (p-value = 0.432). However, when the likelihood ratio was calculated for individual adverse events, the majority of adverse events were found to be more likely to occur in patients who were HIV positive and on HAART, than

Table II: Likelihood ratios of adverse events occurring in patients who were HIV positive and on HAART, compared with those who were not on HAART

Adverse effect	Likelihood ratio
Seizures	4.3
Peripheral neuropathy	1.99
Hearing loss and vestibular disturbances	6.6
Psychoses and confusion	1.91
Gastrointestinal symptoms (nausea, vomiting and diarrhoea)	6.6
Jaundice	1.92
Arthralgia	6.71
Skin rashes	3.3

Table III: Adverse effects of multidrug-resistant tuberculosis treatment, reported by HIV status and concomitant HAART

Adverse effect	Adverse events present prior to multidrug-resistant tuberculosis treatment	Total number affected	Description of patients who developed adverse effects while on multidrug-resistant tuberculosis treatment							
			Adverse events in first six months on treatment	% of unaffected sample that developed adverse events	HIV-positive (p-value)	HIV-negative (p-value)	HIV status not known	HIV-positive, on HAART	HIV-positive, not on HAART	HAART status unknown
Hearing loss and vestibular signs	19	114	95	28.7	77 (0.047)	17	1	67	6	4
Peripheral neuropathy	52	121	69	23.2	56 (0.016)	12	1	50	5	1
Gastrointestinal disturbances, (diarrhoea, nausea and vomiting)	4	75	71	20.5	54 (0.386)	15	3	48	3	0
Arthralgia	29	80	51	15.9	57 (0.163)	21	2	47	7	3
Rashes and dermatological effects (not Stevens-Johnson syndrome)	8	56	48	14.0	37 (0.654)	11	0	34	2	1
Gastrointestinal disturbances, (abdominal pain and dyspepsia)	0	36	36	10.3	23 (0.156)	13	0	21	2	0
Psychoses and confusion	0	29	29	8.3	17 (0.040)	12	0	13	3	1
Poor vision	5	24	19	5.5	16 (0.427)	2	1	14	13	1
Thyroid disease	78	95	17	6.3	12 (< 0.001)	4	0	11	1	1
Renal dysfunction	0	10	10	2.9	9 (0.457)	2	1	8	1	0
Insomnia	0	10	10	2.9	9 (0.462)	1	0	8	1	0
Seizures	1	7	6	1.7	5 (1.000)	1	0	4	0	1
Glycaemic control*	0	5	5	1.4	1	4 (0.143)	0	1	0	0

Adverse effect	Adverse events present prior to multidrug-resistant tuberculosis treatment	Total number affected	Description of patients who developed adverse effects while on multidrug-resistant tuberculosis treatment							
			Adverse events in first six months on treatment	% of unaffected sample that developed adverse events	HIV-positive (p-value)	HIV-negative (p-value)	HIV status not known	HIV-positive, on HAART	HIV-positive, not on HAART	HAART status unknown
Hepatitis/ jaundice	36	39	3	1	2 (0.334)	1	0	2	0	0
Dizziness	0	3	3	0.9	3 (0.309)	0	0	2	1	0
Memory loss	0	3	3	0.9	2	1 (0.755)	0	2	0	0
Headaches	0	2	2	0.6	2 (0.406)	0	0	1	1	0
Darkening of nails	0	1	1	0.3	1 (0.558)	0	0	1	0	0
Disembodied feeling	0	1	1	0.3	1 (0.558)	0	0	1	1	0
Disturbing dreams	0	1	1	0.3	0	1 (0.087)	0	0	0	0
Flu-like illness	0	1	1	0.3	1 (0.558)	0	0	1	0	0
Loss of libido	0	1	1	0.3	1 (0.558)	0	0	1	0	0
Mastodynia	0	1	1	0.3	1 (0.558)	0	0	1	0	0
Painful gums	0	1	1	0.3	1 (0.558)	0	0	1	0	0
Perversion of taste	0	1	1	0.3	1 (0.558)	0	0	1	0	0
Swollen feet	0	1	1	0.3	1 (0.558)	0	0	1	0	0
Finger cramps	0	1	1	0.3	1 (0.558)	0	0	1	0	0
Gout	0	1	1	0.3	1 (0.558)	0	0	1	0	0
Hiccups	0	1	1	0.3	0	1 (0.087)	0	0	0	0

* p-value calculated using only patients with diabetes as a sub-group, n = 15

in those who were not on HAART. Table II lists the likelihood ratios of specific adverse events in patients on HAART.

Patients who were on stavudine (D4T)-containing regimens accounted for 56% (52 cases) of peripheral neuropathy, 40% (20 cases) of nausea and vomiting, and 70% (14 cases) of upper abdominal pain and dyspepsia. Patients on efavirenz (EFV)-containing regimens accounted for 60% (3 cases) of seizures and 92.3% (12 cases) of psychoses or confusion. Twelve patients on regimens containing EFV or nevirapine (NVP) accounted for the majority of cases with skin rashes and dermatological effects (90%).

The most frequently occurring adverse events in descending order of frequency were hearing loss and vestibular disturbance (28.7%); peripheral neuropathy (23.2%); gastrointestinal disturbances, i.e. diarrhoea, nausea and vomiting (20.5%); arthralgia (15.9%); rashes and dermatological effects (other than Stevens-Johnson syndrome) (14%); abdominal pain and dyspepsia (10.3%); and psychoses and confusion (8.3%). Table III lists the frequency of all the adverse effects reported, according to HIV status and concomitant HAART and multidrug-resistant tuberculosis treatment.

Thirty-six patients (10.3%) had abnormal liver enzyme biochemistry prior to initiation of multidrug-resistant tuberculosis treatment. Seventeen of these patients had cholestatic obstruction [(gamma-glutamyl transferase (GGT) > alanine transaminase (ALT)] and 15/17 (93.75%) were on HAART. Fifteen patients had mild hepatitis (ALT five times the upper limit of normal), all of which were on HAART, and four patients had frank hepatitis (ALT 10 times the upper limit of normal), three of which were on HAART. Three patients developed hepatitis while on multidrug-resistant tuberculosis treatment.

Various forms of thyroid disease were found in 95 patients. Seventy-eight patients in the sample (22.3%) had thyroid disease prior to initiating multidrug-resistant tuberculosis treatment, and 17 patients in the sample (4.8%) developed thyroid disease while on treatment. Sixty-five (68.4%) of the 95 affected patients had normal thyroid-stimulating hormone (TSH) levels, with low T_4 (free thyroxine) levels, or "sick euthyroid syndrome". Clinical hypothyroidism was found in 27 patients, two patients had subclinical hypothyroidism, and one patient had subclinical hyperthyroidism. Of the 17 patients who developed thyroid disease while on multidrug-resistant tuberculosis treatment, 12 were HIV positive, and 11 were on HAART.

Ten patients developed renal dysfunction while on treatment. Four had prerenal failure, while six had intrinsic renal failure. Eight of these ten patients were HIV positive and on HAART.

Fifteen patients were diabetic, of whom 6 (40%) experienced at least one episode of worsening glycaemic control or dysglycaemia. HIV status and HAART use were not found to be significantly associated with the dysglycaemia incidence (p-value = 0.143).

Discussion

Adverse events related to certain drugs that were used for multidrug-resistant tuberculosis, e.g. ototoxicity from aminoglycoside use, are well recognised.[13] Less common adverse effects, e.g. severe psychiatric manifestations with the use of cycloserine, have been reported.[14] The WHO has published a list of adverse affects and the drugs with which they are associated, for patients with multidrug-resistant tuberculosis and HIV co-infection who are being managed with anti-tuberculosis drugs and HAART,[7] to assist clinicians.

A few documented international studies investigating the adverse effects of multidrug-resistant tuberculosis treatment in ambulant patients have been conducted in Europe, the Middle East and South America.[8-11] However, these findings may not be applicable in the South African context, because of the high proportion of patients who are co-infected with HIV. Co-morbidity, due to HIV infection and treatment with HAART, may alter the profile of adverse events. Inter-study differences, pertaining to the most common adverse effects that were reported, make these studies difficult to compare. The study conducted in Istanbul, Turkey, from 1992-2004 on 263 patients with multidrug-resistant tuberculosis revealed ototoxicity (42%), psychiatric disorders (21%), gastrointestinal disturbances (14%), arthralgia (11%), epileptic seizures (10%), hepatitis (5%), and dermatological effects (4.5%).[10] By comparison, the study conducted in Lima, Peru, from 1996-1998 on 60 patients with multidrug-resistant tuberculosis reported mild gastritis (100%), dermatological effects (43%), peripheral neuropathy (17%), depression (18%), and anxiety (11%).[11] These studies did not investigate the prevalence of HIV co-infection or the effects of HAART on the adverse events profile. Table IV presents the findings of these cited studies regarding the adverse event profiles of multidrug-resistant tuberculosis treatment in various countries, as well as the WHO guidelines on the adverse events of multidrug-resistant tuberculosis treatment and HAART.

A South African study of 665 in-patients with multidrug-resistant tuberculosis conducted in 2005 in Cape Town, found that among patients who were less than 60 years old, those who were co-infected with HIV were more likely to be admitted with adverse events than those without HIV co-infection.[6] It was also found that within the group that was HIV infected, patients who were receiving HAART were more likely to be admitted with adverse events, than patients who were not on HAART.[6] In this study, only adverse events that were severe enough to warrant admission were studied, and thus may not accurately reflect the adverse events

Table IV: Known adverse effects of HAART and multidrug-resistant tuberculosis

HAART drugs linked to specific adverse events	Anti-tuberculosis drugs linked to specific adverse events	Multidrug-resistant tuberculosis treatment adverse effects (WHO guideline)[12]	Adverse effects reported in other studies[8-11]	Common adverse effects of HAART and anti-tuberculosis treatment[7]
D4T	Terizidone	Seizures	Seizures	Seizures (central nervous system toxicity)
	Aminogylcosides (kanamycin), ethionamide	Peripheral neuropathy	Peripheral neuropathy	Peripheral neuropathy
	Aminogylcosides (kanamycin)	Hearing loss and vestibular disturbances	Hearing loss and vestibular disturbances	
EFV	Ethionamide, terizidone	Psychoses	Psychoses	
EFV	Fluoroquinolones	Depression	Depression	Depression
D4T	Ethionamide	hypothyroidism		hypothyroidism
Protease inhibitors (lopinovir plus ritonavir), D4T, NVP	Ethionamide	Gastrointestinal symptoms other than gastritis (nausea, vomiting and diarrhoea)	Gastrointestinal symptoms other than gastritis (nausea, vomiting and diarrhoea)	Gastrointestinal symptoms other than gastritis (nausea, vomiting and diarrhoea)
All ART drugs	Ethionamide, pyrazinamide	Gastritis (upper abdominal pain or discomfort, dyspepsia)	Gastritis (upper abdominal pain or discomfort, dyspepsia)	
Protease inhibitors (lopinovir plus ritonovir), NVP, EFV	Ethionamide, fluoroquinolones	Jaundice/hepatitis	Jaundice/hepatitis	Jaundice/hepatitis
TDF	Aminogylcosides (kanamycin)	Renal toxicity		Renal toxicity
	Pyrazinamide	Arthralgia	Arthralgia	
			Anxiety	
NVP, EFV, D4T	Ethambutol, pyrazinamide		Stevens-Johnson syndrome	
NVP, EFV, D4T	Ethambutol, pyrazinamide		Skin rashes	Skin rashes
Protease inhibitors (lopinovir plus ritonavir)				Dysglycaemia
	Ethambutol	Visual impairment		

D4T: stavudine, EFV: efavirenz, NVP: nevirapine, TDF: tenofovir

profile experienced by the ambulatory patients.

In our study, the HIV and multidrug-resistant tuberculosis co-infection rate (74.5%) was higher than the rate recently reported in a study based in the Western Cape (34%), which looked at patients who were admitted with multidrug-resistant tuberculosis.[15] The Western Cape study also reported a lower HIV co-infection rate in in-patients with multidrug-resistant tuberculosis, compared with in-patients with drug-sensitive tuberculosis.[15] This difference may reflect the higher HIV disease burden in the KwaZulu-Natal province, or socio-economic differences between the regions. The percentage of patients who were HIV positive on HAART (85%) was also higher than that reported in the Western Cape study (74%).[15] However, it is still below the Department of Health target, which is to have all patients who have multidrug-resistant tuberculosis and co-infected HIV on antiretroviral therapy, if indicated.[2]

In this study, it was necessary to include the occurrence of adverse events prior to initiation of treatment for multidrug-resistant tuberculosis, because adverse events may be due to several factors. These may occur because of the effects of current or previous standard tuberculosis treatment,[12] or as a manifestation of HIV infection itself or HAART use.[7,12] In addition, some drugs that are used to treat multidrug-resistant tuberculosis and HIV can potentially produce similar adverse events.[7] Also, the occurrence of certain adverse events are known to be linked to the use of certain HAART drugs[7] (see Table IV). As one of the objectives of this study was to establish an adverse events profile in the study population, which had not been carried out previously, all adverse events that were recorded in the patient files were included.

According to the current tuberculosis management guidelines, "routine culture and first-line drug-susceptibility testing (DST) should be done for all-high risk groups, such as retreatment patients with tuberculosis, new patients with tuberculosis who remain sputum-smear positive after two months and symptomatic close contact of patients with confirmed multidrug-resistant tuberculosis. Second-line DST should be conducted on all patients with confirmed multidrug-resistant tuberculosis."[4]

This is a point of concern, as the results of this study showed that 45% (158/350) of patients with multidrug-resistant tuberculosis were found to have multidrug-resistant tuberculosis prior to any previous tuberculosis treatment, or while on their first tuberculosis treatment. Thus, usually these patients are not tested for tuberculosis resistance at their initial presentation, unless they are close contacts of confirmed patients with multidrug-resistant tuberculosis. Therefore, most of them are tested two months after starting standard treatment, if they remain sputum-smear positive.

These patients could potentially continue to infect other members of their families and community prior to starting appropriate therapy. A further 40% (143/350) of patients were diagnosed with multidrug-resistant tuberculosis while receiving their first retreatment regimen. This rate is much higher than that reported in other studies, and suggests the need to either implement drug sensitivity testing for all first-time patients with tuberculosis, or find a way to identify high-risk patients when they present with tuberculosis for the first time. In this study, patients presenting with primary multidrug-resistant tuberculosis were statistically more likely to be young females who were HIV positive. However, there was a significant association with positive HIV status and a positive tuberculosis contact history in males with primary multidrug-resistant tuberculosis. Therefore, these subgroups may represent high-risk groups who should be offered drug sensitivity testing on initial presentation.

It was also of concern that there was little available information on the patients' HIV treatment and monitoring in the records. Currently, patients attend HIV clinics near their homes where their treatment cards are held, while also attending the centralised multidrug-resistant tuberculosis clinic. In this study population, information was lacking on CD4 counts and viral loads. The WHO has advocated that multidrug-resistant tuberculosis and HIV treatment be combined at a single clinic to improve the management of both conditions.[7] Since a single laboratory service performs pathology tests for both clinics, using the patient's identification number would also allow doctors and nurses in either clinic to document all results.

In this study, patients who were HIV positive were more likely to experience adverse effects than patients who were HIV negative. This finding is similar to that of a previous South African study.[6] The likelihood ratios for the occurrence of most adverse events was greater in patients who were HIV positive on HAART, compared with those not on HAART, although due to small numbers in these subgroups, this was not statistically significant. In this study, the adverse events profile and the frequencies of the adverse events were dissimilar to those reported in other studies (see Table IV). The overall occurrence of adverse events in patients who were on HAART, compared with those who were not on HAART, was not statistically significant. Thus, the concomitant use of HAART and multidrug-resistant tuberculosis drugs does not conclusively account for differences in the adverse events profile found in our study, when compared with that of other studies. The possibility of under-reporting in this, as well as other studies, must be considered. In the future, under-reporting might be mitigated by the development of a recording instrument, similar to the one that was used to collect data for this study. Such a tool could be used by clinic doctors to quickly and objectively record adverse effects in a standardised way, and prompt clinicians to enquire about certain adverse effects that patients might not have reported.

The association of thyroid disease with tuberculosis is known. Mostly, it is due to rifampicin-induced hypothyroidism[16] and thyroid suppression due to chronic illness. In a few cases, it is due to thyroid tuberculosis. Therefore, there is a need to monitor thyroid functions periodically. In this study, the high percentage of thyroid disease 95/350 (22.3%) was thought to be the result of the direct effects of a chronic disorder, like tuberculosis, on the thyroid and/or the suppressive effect of ethionamide or stavudine on thyroid function.[17,18] In this study, "sick euthyroid syndrome" was the most common finding. In sick euthyroid syndrome,TSH levels are usually normal, with low T_4 levels. The syndrome is thought to be due to the temporary suppressive effects on the thyroid by certain drugs, but it is also independently associated with chronic illnesses, such as tuberculosis.[19,20]

Renal failure in the study group was mild to moderate. No patients required dialysis. In most cases, the dose of kanamycin was reduced in frequency from five injections per week to three, and the patients were monitored carefully.

The incidence of dysglycaemic events in more than a third of the patients with diabetes (80% of which were HIV negative) is not linked to any known adverse effect of multidrug-resistant tuberculosis drugs. However, diabetic treatment compliance, dietary compliance, and a chronic state of ill health are all confounding factors that can affect glycaemic control, and these factors were not controlled in this study.

Conclusion

The high percentage of patients who are found to be multidrug-resistant tuberculosis-positive *de novo,* or while on standard tuberculosis treatment, suggests that drug sensitivity testing for all patients with tuberculosis should be considered. Although all multidrug-resistant tuberculosis cases are probably due to "acquired resistance", i.e. resistance to a drug to which the organism was previously susceptible,[21] it must be considered that some treatment-naïve patients can present for the first time with multidrug-resistant tuberculosis. It was not possible to determine

the extent to which this might have been true in this study population. However, it would be advisable to investigate this further. Fortunately, the GenXpert®, which rapidly detects rifampicin-resistance based on gene profiling of the mycobacterium, is available in a number of hospitals throughout KwaZulu-Natal. Results from this study suggest that there is a need to implement this technology in all institutions in which tuberculosis is diagnosed.

The findings of this study support the current national policy that all patients who have tuberculosis should be tested for HIV, and that all patients who are HIV positive with multidrug-resistant tuberculosis should be on HAART.

Patients who were HIV positive and who are on multidrug-resistant tuberculosis treatment were statistically more likely to experience certain adverse events more so than patients who were HIV-negative. Clinicians need to be vigilant when looking for adverse events, to inform patients of the possibility of adverse events developing, and to manage adverse events in order to encourage patients to remain adherent to their treatment. The reporting of adverse events to the Department of Health should be encouraged, as such reports contribute both to local and global treatment surveillance.

The possibility of under-reporting of adverse events might be mitigated by the development of a standardised recording instrument for use by clinic doctors and nursing staff.

Some of the findings suggested by this study could be confirmed by a case-controlled cohort study, using the three patient subgroups of patients identified, i.e. those with multidrug-resistant tuberculosis only, those co-infected with multidrug-resistant tuberculosis and HIV who were on HAART, and those co-infected with multidrug-resistant tuberculosis and HIV who were not on HAART.

Limitations

As a result of patients attending separate HIV and multidrug-resistant tuberculosis clinics, there was poor recording of current HIV treatment and monitoring results in the multidrug-resistant tuberculosis clinic files. A further limitation was the fact that the recorded adverse events were based on clinical assessments that were made by the treating doctors. Therefore, to some degree, they were subjective. However, reporting in this manner is in accordance with WHO tuberculosis treatment guidelines.

Acknowledgments

We are most grateful to Dr Iqbal Master and Dr Shamin Maharaj, who facilitated access to patient records at the King George V Hospital Multidrug-Resistant Tuberculosis Clinic, and to all the staff and doctors working there. We would like to thank Stephan van de Linde for assistance with the statistical analysis.

References

1. Global tuberculosis control: a short update to the 2009 report. World Health Organization. Geneva: World Health Organization; 2009.
2. Management of drug resistant tuberculosis draft policy guidelines 2009. Pretoria: South African Government Publishing Service; 2009.
3. Drug- and multidrug-resistant tuberculosis (MDR-TB): frequently asked questions. World Health Organization [homepage on the Internet]. c2012. Available from: www.who.int/tb/challenges/mdr/faqs/en/index.html
4. Tuberculosis strategic plan for South Africa, 2007-2011. Health Department, South Africa [homepage on the Internet]. 2007. c2012. Available from: www.info.gov.za/view/DownloadFileAction?id=72544
5. Arbex MA, Varella MCL, Siqueira HR, Mello FAF. Antituberculosis drugs: drug interactions, adverse effects, and use in special situations. Part 2: second-line drugs. J Bras Pneumol. 2010;36(5):641-656.
6. Metha U, Durrheim DN, Blockman M, et al. Adverse drug reactions in adult inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study. Br J Clin Pharmacol. 2007;65(3):396-406.
7. Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update. Geneva: World Health Organization; 2008.
8. Shin SS, Paechnikov AD, Gelmanova IY, et al. Adverse reactions among patients being treated for MDR-TB in Tomsk, Russia. Int J Tuberc Lung Dis. 2007;11(12):1314-1320.
9. Masjedi MR, Tabarsi P, Chitsaz E, et al. Outcome of treatment of MDR-TB patients with standardised regimens, Iran, 2002-2006. Int J Tuberc Lung Dis. 2008;12(7):750-755.
10. Törün T, Güngör G, Ozmen I, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005;9(12):1373-1377.
11. Furin JJ, Mitnick CD, Shin SS, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2001;5(7):648-655.
12. Treatment of tuberculosis guidelines. World Health Organization. 4th ed. Geneva: WHO Press; 2010.
13. Duggal P, Sarkar M. Audiologic monitoring of multi-drug resistant tuberculosis patients on aminoglycoside treatment with long term follow-up. BMC Ear Nose Throat Disord. 2007;7:5.
14. Vega P, Sweetland A, Acha J, et al. Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2004;8(6):749-759.
15. van der Plas H, Mendelson M. High prevalence of comorbidity and need for up-referral among inpatients at a district-level hospital with specialist tuberculosis services in South Africa: the need for specialist support. S Afr Med J. 2011;101(8):529-532.
16. Takasu N, Kinjou Y, Kouki T, et al. Rifampin-induced hypothyroidism. J Endocrinol Invest. 2006;29(7):645-649.
17. Chhabra N, Gupta N, Aseri ML, et al. Analysis of thyroid function tests in patients of multidrug resistance tuberculosis undergoing treatment. J Pharmacol Pharmacother. 2011;2(4):282-285.
18. Satti H, Mafukidze A, Jooste PL, et al. High rate of hypothyroidism among patients treated for multidrug-resistant tuberculosis in Lesotho. Int J Tuberc Lung Dis. 2012 (Epub ahead of print).
19. Chow CC, Mak TW, Chan CH, Cockram CS. Euthyroid sick syndrome in pulmonary tuberculosis before and after treatment. Ann Clin Biochem. 1995;(32) Pt 4:385-391.
20. Camacho PM, Dwarkanathan AA. Postgraduate medicine: sick euthyroid syndrome. [homepage on the Internet]. c2012. Available from: http://postgradmed.org/doi/10.3810/pgm.1999.04.694
21. Hawkey PM. The origins and molecular basis of antibiotic resistance. BMJ. 1998;317(7159): 657-660.