academicJournals

Vol. 9(35), pp. 875-880, 22 September, 2015
DOI: 10.5897/AJPP2015.4298
Article Number: B8C08E355329
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Do HIV infection and antiretroviral therapy influence multidrug-resistant tuberculosis treatment outcomes?

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Received 21 February, 2015; Accepted 1 July, 2015

The aim of this study was to find out whether human immunodeficiency virus (HIV)-infection and antiretroviral drugs influence multidrug-resistant (MDR)-tuberculosis (TB) treatment outcomes. The study compares MDR-TB treatment outcomes between HIV-positive and HIV-negative patients. It involved patients admitted for treatment of MDR-TB between 1 January 2004 and 31 December 2006. From 363 patients selected, 268 (177 males and 91 females) had MDR-TB and 95 patients (59 males and 36 females) were co-infected with HIV. Children in the HIV-negative group were 41 and 7 in the HIV-positive group. The HIV-infection was treated with Stavudine, Lamivudine and Efavirenz in 54 patients. Kanamycin, Ethionamide, Ofloxacin, Terizidone, Pyrazinamide and Ethambutol were used for MDR-TB treatment. In HIV-negative and HIV-positive patients MDR-TB treatment outcomes were, respectively as follows: 37 and 35% cure, 9 and 5% treatment failure, 20 and 25% lost to follow up, 11 and 17% mortality, 19 and 13% treatment completed, 6 and 5% transfer-out. The cure rate was 100% in children. In HIV-positive patients, MDR-TB cure rate was 35% in patients on ARVs and 34% in patients not receiving ARVs. The difference between these cure rates is not statistically significant (p-value = 0.79). The median (range) duration of ART before the start of MDR-TB treatment was 10.5 (1 to 60) months and did not influence MDR-TB treatment outcomes. In children, the full treatment was supervised in hospital. This could explain the 100% cure rate. Adults' treatment was supervised in hospital only during the intensive phase then followed up as out patients over 18 months. According to the results of this study, HIV-infection and antiretroviral therapy did not influence MDR-TB treatment outcomes.

Key words: Treatment outcomes, human immunodeficiency virus, multidrug-resistant tuberculosis, antiretroviral agents.

INTRODUCTION

According to the National Department of Health (DOH) (Department of Health, Republic of South Africa 2011), South Africa is the world's third highest burden tuberculosis (TB) country and ranks the 5th highest with regards to drug-resistant tuberculosis (DR-TB). Furthermore, the numbers of multiple drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) patients have increased due to the concurrent human immunodeficiency virus (HIV) epidemic and inadequate management of TB. MDR-TB is

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defined as resistance of *Mycobacterium tuberculosis* (*M. tuberculosis*) against, at least, isoniazid and rifampicin (Department of Health, 2013). XDR-TB represents a progression from MDR-TB to further include resistance to second line anti-TB drugs, including any fluoroquinolone and at least one of three second line injectables, namely, Kanamycin, Amikacin or Capreomycin (Department of Health, 2013). From 2004 to 2009, there has been a steady increase in the number of cases. In all nine provinces, the total number of MDR-TB and XDR-TB cases was 45196 and 3128, respectively. The most affected provinces were KwaZulu-Natal with 11393 (25.2%) MDR-TB cases and the Western Cape with 10947 (24.2%) MDR-TB cases notified. They were followed by the Eastern Cape and Gauteng Province with 7993 (17.6%) and 6200 (13.7%) cases notified, respectively. Out of 3128 XDR-TB cases, KwaZulu-Natal notified 1499 (47.9%), the Western Cape notified 342 (10.9%), the Eastern Cape 808 (25.8%) and the Gauteng Province 208 (6.6%) (Department of Health, Republic of South Africa 2011). South Africa had the highest reported number of MDR-TB and XDR-TB cases in Africa in 2007 (World Health Organization, 2009).

The increase in notified TB cases has been largely attributed to the concurrent HIV epidemic. An estimated 73% of the reported TB cases in South Africa are among people living with HIV/AIDS (World Health Organization 2009). TB is the leading reported cause of death by natural causes (Statistics South Africa, 2014). The emergence of drug resistance, developing among many other factors, such as poor adherence to anti-TB treatment, has become a serious challenge. Patients with drug resistant TB are more difficult to treat and also have poorer outcomes (Holtz et al., 2006; Nathanson et al., 2006; Kim et al., 2010; Shean et al., 2008; Pepper et al., 2009).

In South Africa, MDR-TB is treated in referral hospitals. In the Province of Western Cape, there are four MDR-TB hospitals. These are Brooklyn Chest Hospital and DP Marais Hospital in the Cape Metropole region, Harry Comay Hospital in the Eden and Central Karoo region and Brewelskloof Hospital (BKH) in the Cape Winelands and the Overberg. According to the national DOH, MDR-TB cure rate is estimated around 30 to 50% (World Health Organization, 2009). There is limited data about MDR-TB treatment outcomes and the prevalence of HIV among MDR-TB patients (Sanchez-Padila et al., 2012). The influence of HIV and the impact of antiretroviral (ARV) drugs and anti-TB drugs on MDR-TB treatment outcomes need to be investigated.

Therefore, the objective of this study was to assess the influence of HIV infection and antiretroviral drugs on MDR-TB treatment outcomes.

METHODOLOGY

The study was conducted at BKH and is a retrospective case control study comparing the treatment outcomes of MDR-TB patients co-infected with HIV (experimental group) and patients infected with MDR-TB (control group). BKH serves approximately 1.3 million people and receives approximately 100 referrals per month.

Patients were included in the study only if they complied with all of the following criteria: (1) those who are MDR-TB sensitive to second line anti-TB drugs with and without HIV infection, (2) those who completed the treatment between 1 January 2006 and 31 December 2008.

The drugs used to treat MDR-TB patients at BKH during the study period include Ethambutol (EMB), Pyrazinamide (PZA), Kanamycin (KAN), Ofloxacin (OFLOX), Ethionamide (ETH) and Cycloserine/Terizodone (CYC/TER). The dosage of each drug was determined according to the patient's body weight.

The data was collected from TB registers and clinical records and entered into a database using Excel (Microsoft Office 2003). The following information was captured: the patient's demographics, his or her age, his or her HIV status, his or her immunological profile, his or her history of previous TB treatment and HIV treatment, and his or her MDR-TB treatment outcomes. The following 2011 World Health Organization (WHO) MDR-TB treatment outcomes were used: cure, treatment completed, failure, default, transfer/moved out, and death. "Cure" was defined as when MDR-TB patient, who has completed treatment according to the guidelines, has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. "Treatment completed" refers to a patient who has completed the treatment, but does not yet meet the criteria to be classified as cured or failure. "Treatment failure" is a situation in which two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. "Default" was used for a patient whose treatment is interrupted for two consecutive months or more. "Transferred"/"moved out" mean that a patient is transferred or moved to another facility to continue treatment. "Death" applies to a patient who, has died for any reason(s) during the course of treatment.

All quantitative variables were analyzed using medians as a measure of location, and range as measure of spread. Nominal variables were descriptively analyzed using frequency distributions indicating the absolute and relative frequencies. The primary outcome was to determine whether there is a difference in "cure", "treatment completed", "treatment failure", "default", "transfer out" and "death" rates between the HIV (+) and HIV (-) groups. For this comparison, the Pearson's chi-square test was used. The degree of freedom is equal to one. With one degree of freedom, the value that must be exceeded to establish significance at the 0.05 level is 3.84.

Ethical approval for the study was obtained from the Ethics Committee of the University of the Western Cape (Ref: 2009/3/18). The permission to conduct the study was granted by the Western Cape DOH. The study was done in accordance with the Helsinki Declaration and confidentiality was observed.

RESULTS

Patient demographics

As indicated in Tables 1 and 2, 363 patients started MDR-TB treatment between the 1st of January 2004 and the 31st of December 2006. They include 268 (74%) MDR-TB patients involving 177 (66%) males and 91 (34%) females, plus 95 (26%) MDR-TB patients who were co-infected with HIV of which 51 (54%) were males and 44 (46%) were females. The number of patients

Table 1. Number of patients per year.

Year	Patients with MDR-TB, Nb (%)			Patients with MDR-TB + HIV, Nb (%)			Total
	Male	Female	Total (M+F)	Male	Female	Total (M+F)	
2006	47 (70)	20 (30)	67 (25)	14 (58)	10 (42)	24 (25)	91
2007	63 (67)	31 (33)	94 (35)	20 (53)	18 (47)	38 (40)	132
2008	67 (63)	40 (37)	107 (40)	17 (52)	16 (48)	33 (35)	140
Total	177 (66)	91 (34)	268 (74%)	51 (54)	44 (46)	95 (26%)	363

Table 2. Age distribution.

Age	Patients with MDR-TB, Nb (%)			Patients with MDR-TB & HIV, Nb (%)			Total
	Male	Female	Total	Male	Female	Total	
0-5	7 (35)	13 (65)	20 (8)	0	0	0	20
6-9	3 (50)	3 (50)	6 (2)	0	1 (100)	1 (1)	7
10-14	10 (67)	5 (33)	15 (6)	3 (50)	3 (50)	6 (6)	21
15-24	22 (69)	10 (31)	32 (12)	5 (45)	6 (41)	11 (12)	43
25-34	44 (66)	23 (34)	67 (25)	13 (59)	99 (41)	22 (23)	89
35-44	48 (66)	25 (34)	73 (27)	18 (51)	17 (49)	35 (37)	108
45-54	30 (79)	8 (21)	38 (14)	6 (55)	5 (45)	11 (12)	49
≥55	13 (76)	4 (24)	17 (6)	6 (66)	3 (33)	9 (9)	26
Total	177 (66)	91 (34)	268	51 (54)	44 (46)	95	363
Total (M+F)	268 (74)			95 (26)		-	363

infected with MDR-TB increased with time in HIV-negative and HIV-positive patients. The number of children in the HIV-negative group was 41 (15.2%) and 7 (7.4%) in the HIV-positive group. The prevalence of MDR-TB was higher between the age of 15 and 55 years.

MDR-TB treatment outcomes

As shown in Table 3, MDR-TB cure rate is 37% in HIV-negative patients and 35% in HIV-positive patients. There is no significant difference (p = 0.4451) in both cure rates. The cure rate was 100% in children.

The other MDR-TB treatment outcome rates in HIV-negative and HIV-positive patients are 9 and 5% failure, 20 and 25% default, 11 and 17% death, 19 and 13% treatment completed, 6 and 5% transfer-out, respectively. The differences between all these outcomes were not statistically significant.

Influence of antiretroviral therapy on the cure rate

Out of 95 HIV (+) patients, 54 (57%) patients were treated with Stavudine, Lamivudine and Efavirenz. The median (range) duration of antiretroviral therapy (ART) before MDR-TB treatment was 10.5 (1-60) months. MDR-TB cure rate is 35% in the group of HIV (+) positive patients on ARVs and 34% in the group not receiving ARVs. The difference between both cure rates is not statistically significant (p-value = 0.79) (Table 4).

All adult patients infected with HIV received Cotrimoxazole (Trimethoprim 80 mg/Sulfamethoxazole 400 mg) 2 tablets daily for PJP prophylaxis regardless of CD4 cell count.

Anti-TB drugs received

In this study, 336 patients ≥14 years old received PZA, EMB, KAN, OFLOX, ETH and CYC/TER for MDR-TB treatment. The other 27 patients, <14 years old, were treated as indicated in Figure 1.

Duration of antiretroviral therapy (ART) before the start of MDR-TB treatment

The median duration of ART before the start of MDR-TB treatment is 10.5 months. It ranges from 1 to 60 months. Viral load or CD4 cell count results were not available.

DISCUSSION

This study compares MDR-TB treatment outcomes between 95 HIV-positive and 268 HIV-negative patients admitted at BKH between January 2004 and December

Table 3. MDR–TB treatment outcomes.

Treatment (Rx) outcomes	MDR-TB patients, Nb (%)			HIV (+) MDR-TB patients, Nb (%)			HIV (+) & (-)
	Male	Female	Total	Male	Female	Total	Total, Nb (%)
Cure	60 (34)	38 (43)	98 (37)	20 (34)	13 (36)	33 (35)	131 (36)
Failures	19 (11)	5 (6)	24 (9)	4 (9)	1 (3)	5 (5)	29 (8)
Defaulted	34 (19)	18 (20)	52 (20)	14 (24)	10 (28)	24 (25)	76 (21)
Died	25 (14)	4 (4)	29 (11)	10 (17)	6 (17)	16 (17)	45 (12)
Rx completed	26 (15)	23 (26)	49 (19)	8 (14)	4 (11)	12 (13)	61 (17)
Transferred out	13 (7)	3 (3)	16 (6)	3 (5)	2 (6)	5 (5)	21 (6)
Total	177 (66)	91 (34)	268 (74)	59 (62)	36 (38)	95 (26)	363

Table 4. Influence of antiretroviral therapy on MDR-TB cure rate.

Variable	HIV (+) patients without ARVs (%)	HIV (+) patients on ARVs (%)	Total
Not cured	27 (66)	35 (65)	62 (65)
Cured	14 (34)	19 (35)	33 (35)
Total	41 (43)	54 (57)	95

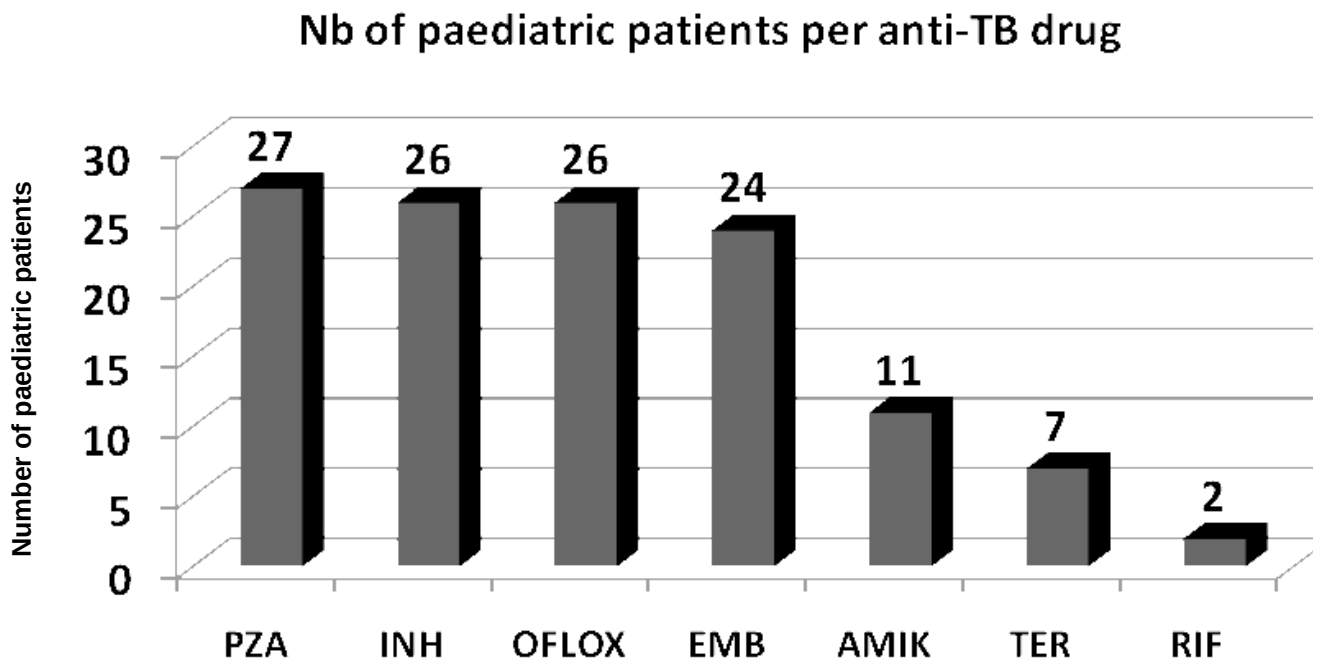

Figure 1. Number of paediatric patients per anti-TB drug.

2006. In both groups, the prevalence of MDR-TB has been significantly increasing during the study period. MDR-TB prevalence is higher in males than females, regardless of their HIV status and affects more of the working class population (25 to 55 years). Statistics from the United States of America, show that TB is a disease that mainly affects those who are 55 years of age and older or of the immuno-compromised people (Kumar et al., 2007).

The total cure rate found in this study (36%) is higher than that found in the same hospital in 2003 (29.4%), 2004 (31.3%) and in 2005 (20%) (Theron, 2003-2005). These findings are consistent with MDR–TB cure rates reported at national level (30 to 50%) in patients without HIV infection in South Africa (Department of Health 2013). This study does not show any significant

difference (p = 0.4451) in MDR-TB cure rate between HIV-negative (37%) and in HIV-positive patients (35%).

The increased percentage of patients (17% HIV-positive and negative) who have completed the treatment, but not yet meet the criteria to be classified as cured, could be a sign of a lack of therapeutic counseling of patients, poor treatment adherence support and weak treatment regimens.

There is no significant difference (p = 0.1779) between the treatment failure rate in MDR-TB patients (9%) and in patients co-infected with MDR-TB and HIV (5%). The failure rates found in this study are statistically not different to those reported in the same hospital in 2003 (5.9%), 2004 (9.0%) and 2005 (4.7%) (Theron, 2003-2005).

The default rate in MDR-TB patients (20%) is statistically similar (p = 0.4264) to the one found in MDR-TB patients co-infected with HIV (25%). However, these rates are unacceptably high and the risk factors associated with them need to be investigated. In a study conducted in South Africa in 2002 (Finlay et al., 2012), it was found that significant risk factors associated with default rate include poor health workers support, changing residence during TB treatment, not receiving adequate counseling about treatment, feeling ashamed to have TB and seeking care from a traditional healer, stopping treatment because the patient felt better, and having a previous history of TB treatment non-adherence. These factors may have contributed to poor treatment outcomes in this study as well.

The relatively low percentage of patients who moved to another facility to continue treatment (6% in MDR-TB patient group and 5% in patients co-infected with HIV) can be seen as a sign of patients' satisfaction about health services at BKH.

The death rate in this study was 11% in MDR-TB patients and 17% in patients co-infected with HIV. No significant statistical difference (p = 0.1837) was found between both groups. At BKH, in 2003, 2004 and 2005, the death rate was 5.9, 9.0 and 24.7%, respectively (Theron, 2003-2005).

Impact of antiretroviral therapy on MDR-TB cure rate

When some HIV (+) patients were involved in the study, they had been on ART for 10.5 (1 to 60) months. The duration of the exposure is long enough to show an interaction between ARVs and anti-TB drugs, if any. The number of studies demonstrating interactions between second-line anti-TB drugs that are used in MDR-TB treatment regimens and ARVS are limited, although the potential for adverse events due to drug interactions is considerable.

It has been demonstrated in this study that HIV infection does not influence MDR-TB treatment outcomes. With the small number of patients involved in this study, assessment could not be done for whether co-infection with HIV exposes MDR-TB patients to more drug toxicities and drug-drug interactions as it was demonstrated by Meintjes (2014).

Furthermore, since there is no difference between treatment outcomes within the group of HIV (+) MDR-TB patients taking ARVs and the group of HIV (+) MDR-TB patients not receiving ARVs, it can be stated that ARV therapy does not influence MDR-TB treatment.

Conclusion

The aim of this retrospective study was to investigate the effect of HIV-infection and ART on MDR-TB treatment outcomes. It was found that neither HIV infection, nor ARVs have an impact on the MDR-TB treatment outcomes at BKH. Furthermore, no drug interactions were found between antiretroviral drugs and second-line antituberculosis agents. MDR-TB treatment outcomes are poor as the cure rate is unacceptably low and the death and defaulter rates are high.

The CD4 counts, viral load, liver function test and renal function tests were not included in the TB register. Therefore, the study could not assess whether the differences in immunological, virological, liver function and renal function profile could affect MDR-TB treatment outcomes.

Therefore, studies involving a higher number of patients subdivided into groups of patients with similar immunological, virological, liver function and renal function profile are needed in order to confirm that HIV infection and changes have any impact on MDR-TB treatment outcomes. Secondly, studies focusing on the risk factors for default, failure and death need to be undertaken. Thirdly, the MDR-TB programme needs to be strengthened considerably and a stronger emphasis must be placed on individual patient counseling and education. Fourthly, tracking systems should be put in place to trace defaulters immediately and address their problems. Last but not least, the patient's family should be involved where possible.

ACKNOWLEDGEMENTS

The authors acknowledged the Department of Health (Province of Western Cape) for the permission to run the study at Brewelskloof Hospital and University of the Western Cape for financial support.

Conflict of interest

Authors have none to declare.

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