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ADVERSE DRUG REACTIONS AMONG HIV INFECTED AND UNINFECTED ADULTS RECEIVING ANTI-TUBERCULOUS THERAPY AT KENYATTA NATIONAL HOSPITAL
J. O. Masese, M. Pharm (Clin. Pharm), Department of Pharmaceutics and Pharmacy Practice, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya, J. R. Rashid, MMed (Inter. Med.), Centre for Clinical Research, Kenya Medical Research Institute, P. O. Box 20778-00202, Nairobi-Kenya, G. D. Nyamu, Pharm (Clin. Pharm), J. N. Ombega, Pharm. and E. M. Mwangangi, M. Pharm (Clin. Pharm) Department of Pharmaceutics and Pharmacy Practice, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya

Request for reprints to: J. O. Masese, Department of Pharmaceutics and Pharmacy Practice, University of Nairobi, P.O. Box 19676-00202, Nairobi, Kenya

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J. O. MASESE, J. R. RASHID, G. D. NYAMU, J. N. OMBEGA, and E. M. MWANGANGI

ABSTRACT

***Background*: Information about the prevalence of adverse drug reactions (ADRs) among HIV infected and HIV uninfected patients receiving anti-tuberculous therapy in Africa is limited due to unavailability of local data or publications and hence the basis of this study.**
***Objective*: To determine the prevalence of adverse drug reactions among HIV infected and HIV uninfected adult patients on anti-TB therapy.**
***Design*: A retrospective cohort study.**
***Setting*: Kenyatta National Hospital, Kenya.**
***Subjects*: HIV infected and HIV uninfected patients receiving anti-TB therapy between January 2006 to December 2007**
***Main Outcome Measures*:Documented adverse drug reactions.**
***Results*: Three hundred and fourteen records were reviewed, 157 for both HIV infected and HIV uninfected. Of the 314 patient files, 96 (30.5%) had ADRs; 70 (44.6%) verses 26 (16.6%) for HIV infected and HIV uninfected respectively. Overall, the most frequent ADR among the two groups was gastrointestinal disturbances (21.7%) verses (10.2%) for HIV infected and uninfected respectively, (RR=2.44 [1.28-4.63], P=0.006). This was followed by peripheral neuropathy (16.6%) verses (4.5%) for HIV infected and uninfected respectively, (RR=4.25 [1.79-10.12], P=0.005). 73(46.49%) of the HIV infected patients were also receiving anti-retroviral therapy, of which 36(49.31 %) of them had ADRs documented. Twenty five (29.8%) of the HIV infected who were not taking anti-retroviral therapy, had ADRs documented.**
***Conclusions*: Gastrointestinal disturbances and peripheral neuropathy were the most common ADRs in both groups. Surveillance systems should be established in hospitals for ADRs monitoring and control.**

INTRODUCTION

A review of literature shows that ADRs from first line anti- TB drugs occurs in both HIV infected and HIV uninfected patients (1). A retrospective study done in London, UK, revealed that serious adverse events (grade III and IV) were recorded in 40% HIV infected and 26% HIV uninfected individuals receiving anti-TB drugs. Peripheral neuropathy and persistent vomiting were more common in HIV-TB co-infected patients. The study further suggested that Africans might not experience ADRs at the same rate as their Caucasian counterparts (2). However, there is no evidence for this argument.

A retrospective study done in Germany on patients receiving first line anti-TB drugs reported that 23% of the patients' treatment had to be interrupted because of ADRs. This study also reported that hepatotoxicity (11%), exanthema (6%) and arthralgia (2%) were the most frequent ADRs (2,3). In a retrospective study conducted in Canada among 430 patients treated for active TB, 1990 - 1999, using first line TB therapy, 46 serious adverse reactions were reported. The incidence of serious side effects, especially hepatitis and

rash, was highest with pyrazinamide, and was associated with female sex, older age and birth in Asia and HIV infection. The consequences of these adverse events included hospitalisations, prolonged therapy, and more clinics and home visits (4,5).

One exploratory Ugandan study indicated that 1% of HIV patients on anti-TB therapy developed hepatotoxicity and 0.8 % had elevated transaminase levels (4.5). All these studies did not estimate the Relative Risk (RR) of developing the ADRs

Despite HIV and TB being prevalent in sub-Saharan Africa, data on the prevalence of ADRs among African adult HIV infected and HIV uninfected patients taking anti-TB drugs was limited (6). This study aimed at determining the prevalence of ADRs in both HIV infected and uninfected African adults receiving ant-TB therapy and subsequently estimation of the Relative Risk of ADRs in these patients.

MATERIALS AND METHODS

Study approval was obtained from Kenyatta National Hospital (KNH) Ethics and Research committee. One hundred and fifty seven adult patients' files of HIV infected and 157 HIV uninfected on anti-TB medications were sampled out of 806 patient files. All the file numbers for HIV-TB co-infected and HIV uninfected TB patients during the study period (January 2006 to December 2007) were retrieved and listed down for each month at the coding section of the hospital's medical records department.

The files were then separated based on the inclusion criteria of the study, which were as follows. Firstly, all adult patient files for either HIV infected or HIV uninfected patients who were diagnosed with TB and started on anti-TB drugs between January 2006 and December 2007. The HIV status and the TB diagnosis were extracted from the patient notes as documented by the treating clinician.

Secondly, patient records with no other chronic infectious diseases or any other major illness for example, cardiovascular and renal. Third, the study considered patients records for first line TB treatment consisting of rifampicin, isoniazid, ethambutol, pyrazinamide and streptomycin. Last, only complete patient files were included in this study.

The exclusion criteria were as follows; First, Patients less than 18 years on the day of TB diagnosis. Secondly, all patients whose HIV status was not documented were excluded from the study. Third, all the patients who had other co-existing chronic infectious diseases or any other major illness for example, cardiovascular and renal. Fourth, incomplete patient files with missing pages resulting in loss of information. Last, patient files whose records documented anti-TB treatment duration of less than seven days of starting intensive phase of TB treatment.

Simple random sampling was used to pick the files for the study. At least seven patient files were randomly picked for each month for both groups. If a given month had less than seven patient files meeting the inclusion criteria for either of the two groups, then all these files were included in the study. The remaining monthly quota was filled by uniformly increasing the number of files sampled in the remaining months of the year(s) of study.

An adverse drug reaction (ADR) was defined according to the World Health Organization (WHO) as 'Any noxious or unintended response to a drug, which occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease or for the modification of physiological function (3).

In this study ADRs considered were peripheral neuropathy, hepatotoxicity, ocular toxicity, gastrointestinal disturbances, cutaneous reactions and ototoxicity. These ADRs were extracted from the patients' records as documented by the treating clinician. These ADRs then formed our dependent variables. The independent variables considered in this study were age of the HIV infected and HIV uninfected patients, anti-TB drugs, anti-retrovirals, gender, education levels, occupation and marital status.

Data quality was assured by using complete files in the study. After data collection were completed, ten (6 %) patient files for each of the groups were reviewed by a co-investigator in five order to compare with the data collected by the principal investigator. The data were then keyed into computer database using Microsoft Access package (MS Access). When data entry was completed, data clean up was done by checking the data entered into the computer database against data recorded in the data collection forms. Any errors identified during data clean up were corrected. The data were analysed using the SPSS® version 13.0 software. Descriptive statistics, frequency and percentage proportions were determined. Tables and figures were presented for important findings Statistical significance was determined using the Pearson Chi -square at $p<0.05$, at 95% confidence level. Continuous variables were compared using t-tests.

RESULTS

Records 314 patients were reviewed of which 157 were HIV infected and 157 HIV uninfected. There was no significant difference in the mean ages for two study groups, (36.7 vs. 35.7) for the HIV infected and uninfected respectively. A total of 83 and 28 ADRs were recorded among HIV infected and HIV uninfected adult patients taking anti-TB drugs, respectively. ADRs were more

common in HIV infected patients 70 (44.6%) compared to HIV uninfected patients 26 (16.6%), (RR = 2.692 [1.819 - 3.985], P < 0.001). More HIV infected than HIV uninfected patients had more than one ADR; 11(7%) versus 2 (1.3%) respectively. (RR=5.50 [1.239 -24.412], p=0.02). Seventy three (46.49%) of the HIV infected patients taking anti-TB drugs were also receiving anti-retroviral therapy, of which 37(50.7%) of them had ADRs documented. Twenty five (29.8%) of the HIV infected who were not taking anti-retroviral therapy, had ADRs documented.

Table 1
Prevalence of specific ADRs among the study subjects

Specific ADRs	HIV status		p value	Relative Risks with corresponding confidence intervals
	HIV Positive N = 157 n (%)	HIV Negative N= 157 n(%)		
GIT disturbances	34(21.7%)	16(10.2%)	0.006	2.44(1.28-4.63)
Peripheral neuropathy	26(16.6%)	7(4.5%)	0.005	4.25(1.79-10.12)
Cutaneous reactions	10(6.4%)	2(1.3%)	0.02	5.27(1.14-24.47)
Hepatotoxicity	9(5.7%)	2(1.3%)	0.03	4.71(1.23-22.17)
Ocular toxicity	3(1.9%)	1(0.6%)	0.3	3.03(0.313-29.54)
Ototoxicity	1(0.6%)	0(0%)	0.3	-

Gastrointestinal disturbances and peripheral neuropathy were the most common ADRs encountered. These were more prevalent in HIV infected than HIV uninfected patients.

Table 2
Prevalence of ADRs and interventions undertaken in the study groups

Specific Adverse drug reaction	HIV infected N = 157) n (%)	HIV uninfected N = 157) n (%)	Interventions
A. Hepatotoxicity	9 (5.7 %)	2(1.3%)	Anti-TB medication, ARVs stopped
B. Peripheral neuropathy	26 (16.6%)	7 (4.5%)	Pyridoxine
C. Ocular toxicity	3 (1.9%)	1(0.3%)	Referral for ophthalmological review
D. Gastrointestinal disturbances	34 (21.7%)	16 (10.2%)	Loperamide, Metoclopamide, Intravenous fluids.
E. Cutaneous reactions	10 (6.4%)	2 (1.3%)	Anti- TB stopped
F. Ototoxicity	1(0.6%)	0	Streptomycin stopped.

DISCUSSION

Our study revealed that adult HIV infected patients receiving anti-TB were at least two times (RR=2.692 [1.819-3.985]) more likely to develop ADRs than their HIV uninfected counterparts having the same treatment. This was in line with previously study that have reported ADRs of anti-TB drugs were comparatively more frequent in the HIV infected patients taking anti-TB drugs (1,7). There are few comparative studies on ADRs among HIV infected and HIV uninfected adult patients taking anti- TB drugs. Furthermore, the few studies done reported only the prevalence rates of ADRs and not the RR (1,2,6,8,9) of developing the ADRs. Consequently, this study calculated the RR for specific ADRs to show the likelihood of the patients in the two groups of developing the ADRs. In our study 50.7% of the HIV infected patients on anti-TB therapy and anti-retroviral therapy (ARvs), documented ADRs compared to 29.8% of the HIV infected patients on anti-TB therapy but not on anti-retroviral therapy. This was in agreement with previous studies that have reported increased

prevalence of ADRs in patients receiving anti-retroviral therapy (11). Consequently, patients co-infected with HIV and TB should be monitored for ADRs.

HIV infected patients taking anti-TB drugs were at least four times (RR= 4.71 [1.23-22.17]) more likely to develop hepatotoxicity than their HIV uninfected counterparts. A retrospective study done by Breen *et al*., reported no difference in the prevalence of hepatotoxicity among HIV infected and HIV uninfected adult patients taking anti-TB drugs (2). The difference in study results may reflect the difference in study criteria, as Breen *et al*., only considered grade III and IV ADRs. In our study the treating clinicians did not grade the ADRs in the patient notes. The confidence interval from our findings is large; therefore, more prospective studies are needed to confirm the RR for developing hepatotoxicity.

Peripheral neuropathy was at least four times more likely to develop in adult HIV infected patients receiving anti-TB drugs than their HIV uninfected counterparts (RR= 4.25[1.79-10.12]). This was in agreement with other previous studies which also suggested that HIV infected patients were more prone to developing isoniazid-induced peripheral neuropathy (2,7,11). Although a number of risk factors for isoniazid induced peripheral neuropathy have been reported elsewhere (2,12) including the poorly nourished, extent of disease, alcoholics, diabetics, uraemic patients and pregnancy, our study had a low proportion of alcohol use and pregnant women thus making assessment of these risk factors unfeasible. Gastrointestinal disturbances were the most commonly recorded ADR in both the study groups. Our study findings revealed that adult HIV infected patients taking anti-TB drugs were at least two times (RR= 2.44 [1.28-4.63]) more likely to develop gastrointestinal disturbances than their HIV uninfected counterparts. Nevertheless, it should be noted that this study was unable to assign all cases of this condition to anti-TB drugs, as other likely causes of gastrointestinal disturbances were not investigated in this study. Furthermore, in this study 62% of the HIV infected patients who developed this condition were also taking ARVs, a possible cause of gastrointestinal disturbances.

Our findings suggested that adult HIV infected patients taking anti-TB drugs were at least five times (RR=5.27 [1.14-24.47]) more likely to develop cutaneous reactions than their HIV uninfected counterparts. All anti-TBs and majority ARvs have been reported to cause a skin rash (13). Consequently, where anti-TB and ARvs were given together, it was difficult to pinpoint a particular drug as the cause of cutaneous drug reaction. The confidence interval from our findings is large; therefore, further studies are needed in this area.

It is well documented that ocular toxicity is uncommon (7,12,14,15). However, data on comparative studies on ocular toxicity among HIV infected and HIV uninfected adult patients taking anti-TB drugs are limited. Although, our study reported no difference in RR for developing ocular toxicity between the two groups: these findings should be interpreted with caution, further studies are needed in this area.

Only one HIV infected patient developed ototoxicity. This was in line with previous studies (16) that have reported ototoxicity to be uncommon. In our study, only a small proportion of our study patients were on the streptomycin containing regimen. Therefore, it was impossible to assess risk estimate for developing ototoxicity between the two groups. Consequently, any conclusions based on one rare case might be misleading and, therefore more large sample-sized studies are required to establish RR of ototoxicity in similar cohort.

It is important to note that the rates of under reporting in the files might have been similar regardless of the HIV status. Furthermore, these findings might not represent the RR estimate of developing ADRs among HIV infected and HIV uninfected children taking anti-TB drugs.

In conclusion, ADRs were more likely to occur in HIV infected African adults taking anti-TB therapy than their HIV uninfected counterparts. Gastrointestinal disturbances and peripheral neuropathy were the most common ADRs among both the two groups. Adverse drug reaction surveillance systems should be established in hospitals. Prospective studies are needed in the future.

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