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Evaluation of Antiretroviral-Related Problems and Interventions by the Clinical Pharmacist in Hospitalized HIV-Infected Patients At Omdurman Management And clinical unit of HIV/AIDS Center (OMACU) Sudan, Khartoum, Omdurman

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ABSTRACT

The aim of the study was to identify antiretroviral-related problems in the prescribing of medication to Sudanese HIV-infected inpatients and to determine the degree of acceptance of the pharmacist's interventions. This study was carried out at Omdurman Teaching Hospital (**OTH**) by a clinical pharmacist trained in HIV pharmacotherapy for one year prospectively. The interaction of antiretroviral was checked for contraindicate combination. Inpatient antiretroviral prescriptions were compared with outpatient (hospital records) dispensing records for reconciliation. Renal and hepatic functions were monitored to check dose adjustments whenever it is needed. The prescriptions for 100 admissions (80 patients) were reviewed. Thirty antiretroviral-related problems were identified in 40 patients (50%). The most common problem was contraindicated combinations (n=10; 33.33%), followed by incorrect dose (n=5;16.7%), dose omission (n=4;13.3%), lack of dosage reduction in patients with renal or hepatic impairment (n=4;13.3%) ,omission of an antiretroviral (n=3; 10%), incorrect schedule according to outpatient treatment (n=2 ;6.7%),prescriptionofalternativeantiretroviraldrugs(n=2;6.7%).Fifteen out of 20 errors were made during admission. A multivariate analysis, the factors associated with an increased risk of HAART-related problems ,were renal impairment OR 4; 95% confidence interval (CI) 1.400 to 11.320, treatment with lopinovir (OR 3.75; 95% CI 0.0198 to 50.44) and admission to a unit other than an infectious diseases unit (OR2.515; 95% CI 0.0300 to 5.00). Prescription1.5 to7.558 of a nonnucleoside reverse transcriptase inhibitor was a protective factor (OR 0.30; 95% CI 0.1339 to 0.850). Ninety per cent of the pharmacist's interventions were accepted. Antiretroviral-related errors affected more than one-in-three patients. The most common causes of error were contraindicated or not recommended drug–drug combinations and dose-related errors. A well-trained clinical pharmacist would help to detect medication problems and promote for antiretroviral drugs use rationally

Keywords: antiretroviral drugs, HIV-infected inpatients

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INTRODUCTION

The view of HIV/AIDS prevalence for the 31 million Sudanese population is1.6% and It is estimated that 320,000 people are living with HIV/AIDS, The actual registered number of HIV cases is only 17,000 at Omdurman Management And clinical unit of HIV/AIDS OMACU center at Sudan, Khartoum, Omdurman which is Established in 2003, by Sudan National AIDS Program(SNAP), as a clinical management &Volunteer Counseling and Testing VCT center for people living with HIV/AIDS & clients seeking testing, VCT was offered to more than 1007 clients,1340 adult living with HIV/AIDS& 305 children were enrolled in HIV care,786 of them (adult & children) had got free access to ARVs & Co-trimoxazoleprophylaxis. The center follows strictly WHO guidelines for management of People living with HIV/AIDS.As previous literature show that hospitalized patient were at high risk of accidental prescribing errors on admission.[1,2]and the people living with HIV are one of them when they are on treatment with highly active antiretroviral therapy (HAART) and hospitalized because the(HAART) themselves are not simple regimens and drug interaction may take place and lead to either patient toxicity or resistance[3].And on discharge resolving this error will be a problem if they are not managed well. Missing antiretroviral dose lead to low levels, the virus can replicate and resistance to treatment can appear. While, toxicity can occur due to an interaction and leads to increased antiretroviral concentrations or the patient receives a higher dose than the correct one. Both of them take place if the prescribing errors not detected in the right time before discharge. Confirming that HAART-related errors are common in hospitalized patients and that admission of an HIV-infected patient by a physician not specialized in infectious diseases could be a risk factor for drug-related error as many author go through [4].

The aims of this study were to identify and describe HAART-related errors in medication prescribed to HIV-infected patients admitted to Omdurman Teaching Hospital and to ascertain the degree of acceptance of the pharmacist's interventions.

MATERIALS AND METHOD

An observational, prospective, follow up study was conducted by a clinical pharmacist trained in HIV pharmacotherapy and supported by a staff pharmacist (between 1 January and 31 December 2010), (on Tuesday and Thursday), biweekly. The patients included are of 18 year’s old or more and admitted to Omdurman Teaching Hospital clinic in Khartoum, Sudan and prescribed HAART.A list was made of all inpatients that were prescribed antiretroviral drugs. Admissions made on other week day were recorded on next day afternoon.

The following data were documented for all patients: age, gender, risk factors for HIV infection, admitting service, serum creatinine level and liver function tests such as serum albumin, total bilirubin, transaminases. For those patients with creatinine value more than 1.2 mg/dL, the glomerular filtration rate was calculated using the Cockcroft–Gault equation [5]. For those patients with any abnormal liver function test value, the admission report was checked to know whether they had cirrhosis [6,7]. Concurrent medication was reviewed twice weekly to check for drug–drug interactions.

HAART errors were classified as follows: contraindicated or not recommended drug–drug combinations, incorrect or incomplete antiretroviral regimen, omitted dose, incorrect dose lack of dose reduction for renal or hepatic dysfunction and incorrect schedule [8].

In Sudan, HIV-infected patients take their antiretroviral medication from VCT center pharmacy unit of the hospital Hence, it was easy for us to determine the patient's HAART regimen. Patient records are allowed for the pharmacist at Omdurman Teaching Hospital and they can easily follow them .Those record were revised with the internal admission prescription to check drug inter action or prescription error before discharge

Drug–drug interactions were checked for contraindicated or not recommended combinations using national and international HIV guidelines [9–11]. If a problem was detected, the pharmacist phoned the attending physician or added a footnote with a recommendation to the manual prescription, so that the attending physician would see it the next day. The acceptance of the pharmacist's recommendations was checked during the next days. If the error was not corrected by the physician within 48 h of the recommendation, the intervention was considered as not accepted.

Data were entered into an Access 2.0 database (Microsoft Corp., Redmond, WA, USA).

Statistical analysis

For the descriptive analysis, qualitative variables were expressed as percentages and frequencies; quantitative variables were expressed as the mean (standard deviation SD). Fisher's exact test was employed to analyze contingency tables. Odds ratios (ORs) for risk factors associated with HAART-related problems were analyzed using generalized estimating equation model. This multivariate model considers the correlation between different admissions belonging to the same patient. The statistical analysis was performed using SPSS Software

RESULTS AND DISCUSSION

80 patient (out of 100 admissions) living with HIV at Omdurman Teaching Hospital who received prescriptions and reviewed over one year.

Table 1. Show the demographic characteristics of these patients. The distribution of admissions by wards was as follows: General Medicine unit, 53(53%); other medical units, 18(18%); surgery wards, 28 (28%); and 1(1%) intensive care units.

Table 1: Demographic characteristics of hospitalized patients receiving antiretroviral therapy (n=80)

Variable	HAART-related errors				P-Value
	Yes		NO		
Male n (%)	20(25%)		34(42.5%)		0.174
Female n (%)	6(7.5%)		20(25%)		
Age (years)	47 ± 11	45 ± 10†	47 ± 11	45 ± 10†	0.230
Risk group n (%)§					
Injecting drug use	0(0)		0(0)		0.362
Heterosexual	10(12.5)		35(43.75)		
Homosexual	10(12.5)		40(25)		
Other	3(3.75)		5(6.25)		

A total of 30 antiretroviral drug-related problems were identified in 40 patients (50% of the admitted patients had at least one antiretroviral problem).

The types of HAART-related errors found are shown in Table 2. The most common problem was contraindicated combinations (n=10; 33.3%), followed by incorrect dose (n=5;16.7 %), dose omission (n=4; 13.3%), incorrect schedule according to outpatient treatment (n=4; 13.3%) lack of dosage reduction in patients with renal or hepatic impairment (n=3 , and n=1; respectively), omission of an antiretroviral (n=3;10%), and addition of an alternative antiretroviral (n=2; 6.7%),incorrect schedule according to outpatient treatment .Fifteen out of 20 errors were made during admission..

Table 2: Types of highly active antiretroviral therapy (HAART)-related problems

Type of error	Number of patients*(n=40)	% of all errors (n=30)
Contraindicated combination	10	33.3%
Incorrect dose	5	16.7%
dose omission	4	13.3%
lack of dosage reduction LF	1	3.3%
lack of dosage reduction RF	3	10%
omission of ARV	3	10%
addition of alternate ARV	2	6.7%
incorrect schedule OPT	2	6.7%

Table 3: The ART error detected

Type of error	Description
Contraindicated combination (n=10)	Patients were prescribed omeprazole while receiving lopinoavir (n=8)
	A patient treated with efavirenz began flucconazole (no dose adjustment data from pharmacokinetic studies were available at the time) (n=1)
	A patient treated with lopinavir/ritonavir was prescribed rifampicin (n=1)
Incorrect dose of an antiretroviral agent (n=5)	A patient was prescribed Nevirapine 200 mg qd when his current regimen was 400 mg qd (n=1)
	A patient was given lopinovir133.3gbd . His current regimen was 1500 mg qd (n=1)
	A patient with renal reduced function was prescribed lamivudine 50 mg qd. His current regimen was 25 mg (n=1)
	A patient was prescribed Zidvudine 150mgbid. His current dose was 300 mg/day (n=1)
	A patient was prescribed efavirenz 200 mg qd instead of 600 mg qd (n=1)
Lack of dose reduction in patients with renal or hepatic impairment (n=4)	A patient with hepatic cirrhosis Child C was prescribed efavirenz 600 mg qd. Efavirenz is contraindicated in Child C patients .Plasma concentrations were not determined (n=1)
	A patient was prescribed lamivudine 300 mg qd. His current dose was 25 mg qd (he was undergoing dialysis) (n=1)
	A patient was prescribed lamivudine 300 mg qd. He had renal impairment and the correct dose adjusted to renal function was 150 mg (n1) A patient was prescribed stavudine 30mg bid. The correct dose adjusted to renal function was 20mg bid (n1)
Antiretroviral dose omitted (n=3)	Patients were prescribed lamivudine 1 tablet qd (the dose was not specified) (n=2)
	Patients were prescribed stavudine 1 tablet bid (the dose was not specified) (n=1)
	A patient whose current regimen was stavudine, lamvudine, neverapine was not prescribed neverapine (n=1)
	A patient whose current regimen was tenofovir, lamvudine, efavirenz and efavirenz was not prescribed (n=1)
Prescription of an antiretroviral that was not part of the patient's current regimen (n=2)	A patient whose current regimen was tenofovir, lamvudine, efavirenz as fixed dose comination and efavirenz was gien twice as single dose(n=2)
Incorrect schedule (n=2)	A patient treated with lopinvir was prescribed one tab at breakfast and the other at dinner instead of both capsules at the same time (n=1)
	A patient was prescribed 2 tablets of neverapine+lamivudine+zidovudine at breakfast instead of 1 tablet bid (n=1)

bid, twice daily; qd, once daily; tid, three times a day

Almost all the antiretroviral-related errors occurred at admission (20; 50%). The error occurred in the HIV clinic in only five cases and was not resolved on admission (four cases of lack of dosage reduction in patients with renal impairment; one case of a contraindicated interaction).

Of 80 admissions to services other than infectious diseases in which antiretroviral agents had been prescribed,

20 had at least one antiretroviral drug-related error (25%), compared with 20 out of 40 admissions in the infectious diseases unit (50%).

In the multivariate analysis, the factors associated with an increased risk of HAART-related problems (Table 4) were renal impairment OR 4; 95% confidence interval (CI) 1.400 to 11.320, treatment with lopinovir (OR 3.75; 95% CI 0.0198 to 50.44) and admission to a unit other than an infectious diseases unit (OR2.515; 95% CI 0.0300 to 5.00). Prescription1.5 to7.558 of a nonnucleoside reverse transcriptase inhibitor was a protective factor (OR 0.30; 95% CI 0.1339 to 0.850). No statistical relationship was found between HAART-related problems and the following factors: age, sex, risk group, liver impairment, nucleoside reverse transcriptase inhibitor-based HAART, a protease inhibitor other than lopinovir, and being treated with an antiretroviral with different presentations.

Table 4: Adjusted odds ratios for risk factors associated with a highly active antiretroviral therapy (HAART)-related error

Variable	Adjusted odds ratio	95% CI	P-value/100
Renal impairment			
No	1		1
Yes	4	(1.400 to 11.320)	
NNRTI			
No	1		1
Yes	0.3	(0.1339 to 0.850)	
Lopinovir			
No	1		1
Yes	3.75	(1.5 to7.558)	
Service			
Infectious diseases	1		1
Other	2.515	(0.0300 to 5.00)	

CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor.

The most common intervention by the pharmacist was a footnote on the prescription (15 of 30; 50%), followed by a telephone call to the attending physician (10 of 30; 33.33%) or nurse 5 of 30; 16.66%).The pharmacist made an intervention in all of the 30 errors detected. This was well accepted in most cases (27 of 30; 90%), and the error was resolved. three interventions were not accepted 10%): lack of dosage reduction in patients with renal impairment (one cases), lack of Efavirenz dosage reduction in a patient with hepatic impairment (one case), and a contraindicated combination (lopinavir and omeprazole; one case)

For the 100 hospitalized HIV infected patient at Omdurman teaching hospital only 80 of them were followed in the outpatient clinic and were checked for their treatment and ART regimen drug related problems and for the first visit after discharge 4.2(95% CI 3.1-5.2)and potential drug related problems found for them (3per patient)most due to drug interaction. After pharmacist intervention and revision of those patient reports before and after the study for the same patient decreased to 3.2(95% CI 3.3-5.1) p0.043. Variation of HIV viral load before and after the study were not detected .The mentioned pharmacist intervention was done an average of 2.3intervention per patient. As all the accepted intervention were reported but the compliance with them did not detect further.

DISCUSSION:

During hospital admission drug related problems were common by evidence for antiretroviral regimens. Moket al. [4] .In another study which indicate that 86% of the patient had at least one problem associated with ARV regimen over four months Pstikia et al.[12]another study also show that there was at least one error in 72% of cases .Purdy et al[13].in hospitalized HIV- infected patients who was followed for 34 month108 significant antiretroviral prescribing error was detected Rastegar et al[13] .Also 25.8%antiretroviral error was detected over one year Heloon et al.3Adding that about 21%of hospitalized HIV patient get 73 HAART errors in 41 patient .while in this study 50% of people living with HIV admitted to Omdurman Teaching Hospital and prescribed Antiretroviral therapy had at least75% medication problem or error related to their regimen which take place during admission .these result match what Rastegar et al and Heelon et al .The most common problem is contraindicated combinations that lead to interactions between the drugs. Mok et al [4] followed by incorrect dose 16.75% like Rastegar (20.4% of all problems)[14] and about 13.3 for does omission and lack of dose adjustment in renal and hepatic impairment while in correct schedule and alternative prescription take place about 6.7%.the total of dose related problem account that about 43.4%of all errors this match Mok et al4and Grayet al [15].

Risk factor association not match any of reviewed studies the causes of HIV medication errors in MEDMARX, a voluntary database reporting inpatient medication errors. They found that the most common causes of error were inappropriate dosing (38%), followed by incorrect medication (32%). In this Study the result was higher than Moket al. [4].for interactions caused by contraindicated or not recommended drug–drug combinations (33.3%) as the result, In total dose related problems (incorrect dose, dose omission, and lack of dose adjustment in patients with

renal or hepatic impairment) in total16.7%of all errors when comparing this result to those of Moket al. [4] and Gray et al. [15] its moderate.

To detect the role of clinical pharmacist intervention or pharmaceutical care done to the HIV in this study we make use of direct measure as viral load and CD4 count (the clinical outcome) and the indirect measure of drug related problem.

Also there is a significance increase in CD4T lymphocyte count for the patient after the study and the clinical pharmacist intervention and follow up after the study period p0.0015 with the retrospective check for their CD4 show no significant difference before the study as it kept constant.as the patient having the pharmaceutical care done by the clinical pharmacist after the intervention there is a significant increase in CD 4 count when compared before and after the study as the HIV patient record are kept at the VCT clinic pharmacy with their detailed data and monthly follow up.

For the 100 hospitalized HIV infected patient at Omdurman teaching hospital only 80 of them were followed in the outpatient clinic and were checked for their treatment and ART regimen drug related problems and for the first visit after discharge 4.2(95% CI 3.1-5.2)and potential drug related problems found for them (3per patient)most due to drug interaction. After pharmacist intervention and revision of those patient reports before and after the study for the same patient decreased to 3.2(95% CI 3.3-5.1) p0.043. Variation of HIV viral load before and after the study were not detected

The mentioned pharmacist intervention was done an average of 2.3intervention per patient. As all the accepted intervention was reported but the compliance with them did not detect further

Risk factors are varying according to the result. This study have limitations that it was not carried on a daily base only done twice per week and the monitoring method was not allow to follow all dose related problems so the clinical outcomes not intended as not all the dispenser and prescriber included daily. Most of the patients are well educated about their regimens.

CONCLUSION

pharmacist trained in HIV pharmacotherapy or a clinical pharmacist play a great role in reducing prescription related error which are common among people living with HIV-who are hospitalized and prescribed HAART regimen that is(one in five patient).The most common issues were contraindicated or not recommended drug–drug combinations and dose related errors. Factors associated with an increased risk of such problems were renal impairment,

receiving lopinanavir, and admission to a unit other than an infectious diseases unit. Receiving nonnucleoside reverse transcriptase inhibitors was a protective factor.

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