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OCCURRENCE OF ADVERSE DRUG REACTIONS ASSOCIATED WITH HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY AT MBAGATHI DISTRICT HOSPITAL, NAIROBI, KENYA
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ABSTRACT

***Background*: Life-saving highly active anti-retroviral therapy (HAART) has been accompanied by the challenge of incident adverse drug reactions (ADRs). Locally generated data is scanty, inadequately documented, and therefore not available to inform revision of clinical protocols.**
***Objective*: To study and document the magnitude and type of ADRs associated with HAART over a 42 month period at Mbagathi District Hospital (MDH) Nairobi.**
***Design*: A retrospective cohort study.**
***Setting*: A high burdened HIV comprehensive care clinic based at the Mbagathi District Hospital in Nairobi, Kenya.**
***Subjects*: HIV infected patients receiving highly active anti-retroviral therapy (HAART)**
***Results*: Adverse drug reactions associated with HAART occurred in 63% of adult study subjects. Majority (91.4%) of the ADRs experienced were medium to long term conditions, namely peripheral neuropathy in 33.3%, lipodystrophy in 32.6%, hepatic toxicity in 24.4% and lactic acidemia in 4.1 % of patients. Furthermore, occurrence of all the ADRs was associated with increasing baseline age ($p<0.0001$). Gender differences were found in patients with lipodystrophy ($p<0.001$), and lactic acidemia ($p=0.047$), with a female preponderance.**
***Conclusion*: Adverse drug reactions were experienced by 63% patients on HAART. Majority of the ADRs were those commonly associated with the medium to long term use of stavudine and nevirapine. Despite the high frequency of ADRs, patient outcomes were favourable as there were no reported deaths or hospitalisations.**

INTRODUCTION

The past decade has seen the introduction of highly active anti-retroviral therapy (HAAR T) which has dramatically reduced morbidity and mortality from HIV - related complications and improved the quality of life among HIV infected patients worldwide (1). However, HAART has been associated with incident of adverse drug reactions (ADRs) (2). Adverse events are the key underlying factors to therapy change or non-adherence to medicines (3, 4). Patients with ADRs are nearly 13 times less likely to have 95-100% adherence and likely to experience three and a half times increased risk of virologic, immunologic and clinical failure. (5).

The occurrence and magnitude of ADRs in developed countries is well documented, while this is not the case in developing countries. In this regard, locally generated data are required to improve clinical protocols and outcomes in Kenya. This study examined ADRs associated with HAART in adult study subjects and their possible risk factors over a 42 month period in a high burdened public health facility, the Mbagathi District Hospital, Nairobi.

MATERIALS AND METHODS

This was a retrospective cohort study design. It examined the clinical encounters of patients managed at the MDH over a three and a half year period (from mid 2003 to the end of 2007). By December 2007, over 7,374 patients had registered to receive comprehensive HIV care and out of this number, 4,034 patients were on HAART. The HAART regimens used at the hospital complied with the Kenya National HAART Guidelines (6) that predominately utilise stavudine based regimens.

Stratified random sampling proportional to size of the adult HAAR T population was used to select the study subjects. Data on bio-demographic, clinical and immunologic parameters, treatment regimens, duration of treatment to experiencing ADRs, types of ADRs experienced and the outcome of the ADRs were extracted from the study subjects' medical records. These data were analysed using Statistical Package for Social Sciences (SPSS) TM version 12.0 for Windows. Descriptive statistics, Chi-square test of statistic, bivariate comparisons of baseline continuous symmetric characteristics, linear mixed-effect models were used to characterise the experienced ADRs, establish change in continuous variables (such as CD4 counts, weight and age), and determine statistical associations and levels of significance. The analyses characterised the number and type of adverse reactions, computed odds ratios, and determined risk for occurrence of the ADRs and possible significant risk factors associated with ART.

Ethical clearance was granted by the committees of Kenyatta National Hospital and College of Health Sciences, University of Nairobi and the Ministry of Science and Technology.

RESULTS

A total of 414 adult study subjects were sampled from 4,034 patients on HAART. These study subjects had a mean baseline age and weight of 34.1 years (standard deviation (sd)±7.84) and 57.9 Kg (sd ±10.6) respectively. Using random sampling with stratification by gender, the study subjects comprised 65.9% (272/413) female patients and 34.1% (141/413) males. About 68.6% (179/261) of patients with ADRs were females, while 31.4% (82/261) were males patients. Despite this finding gender was not a significant risk factor in the occurrence of ADR, p=0.127 (Table 1).

Sixty percent (154/259) of patients with ADRs had been commenced on D4T30/3TC/NVP (Table 1). The second highest (n= 69, 26.6%) number of patients with ADRs were patients on D4T40/3TC/NVP. Seventy seven percent (1191154) of patients with ADRs and commenced on D4T30/3TC/NVP were female while 22.73% (351154) were males. Among patients with ADRs started on D4T40/3TC/NVP, 60.87% (42/69) were females and 39.13% (27/69) were males. Similarly, the one female patient started on AZT based regimen also experienced an ADR.

Eighty six percent (223/259) of patients with ADRs had been commenced on NVP based regimens while 13.9 % (36/259) were on EFV based regimens (Table 1). Among the females with ADRs, 91.2% (1651181) were on NVP based regimens, while 8.8% (161181) were on EFV based regimens. Among the males with ADRs, 75.61 % (62/82) of patients were on NVP based regimens while 24.39% (20/82) were on EFV based regimens.

Table 1

Comparison of Existence of ADRs with Patient Bio-Demographic and Immunological Factors

		Patients who had ADRs		P –values
	Total no. %	No no. (%)	Yes no. (%)	
Gender N=413				
- Male	141(34.14)	59(38.82)	82(31.42)	Referent
- Female	272(65.86)	93(61.18)	179(68.58)	0.127
Marital status N=410				
- Married	189(46.10)	72(47.37)	117(45.35)	Referent
- Single	110(26.83)	41(26.97)	69(26.74)	0.888
- Widowed	69(16.83)	20(13.16)	49(19.0)	0.178
- Divorced	42(10.24)	19(12.50)	23(8.91)	0.392
WHO stage N=412				
Stage 1 and 2	39(9.47)	13(8.55)	26(10.00)	Referent
Stage 3	325(78.88)	123(80.92)	202(77.69)	0.582
Stage 4	48(11.65)	16(10.53)	32(12.31)	0.999
ART regimen at baseline N=410				
D4 T30/3 TC/NVP	240(58.25)	86(56.21)	154(59.46)	Referent
D4 T30/3 TC/EFV	43(10.44)	15(9.80)	28(10.81)	0.905
D4 T 40/3 TC/NVP	116(28.16)	47(30.72)	69(26.64)	0.392
D4 T40/3 TC/EFV	13(3.16)	5(3.27)	8(3.09)	0.894

Types of Adverse Drug Reactions: Sixty three percent (95% CI 58.4-67.7%), of patients experienced one or more ADRs during the study period (Table 2). Exactly, 64.4% (168/261) of study subjects who manifested a reaction had one ADR, 26.5% (69/261) had two, while 9.3% (24/261) had three different types of ADRs within the study period.

When all the ADRs were considered collectively, binary logistic regression model revealed significant correlation between occurrence and increasing baseline age (p<0.0001) but not with baseline CD4 cell counts (p=0.944). For every additional year at baseline, the probability of experiencing an ADR increased by 7.6 % (OR 1.076, 95% CI 1.044- 1.108, p< 0.0001).

Hepatic toxicity, lipodystrophy, lactic acidosis and peripheral neuropathy were the key medium to long term adverse reactions experienced by patients in the study period. They collectively comprised 91.4% (391/428) of all the incidents of ADRs and had an incidence rate of 49% per 100 person years. About 33% of patients (n=138, 95% CI 28.8-37.9%) had peripheral neuropathy, while lipodystrophy occurred in 32.6% (n=135, 95% CI 28.07- 37.14%) and hepatic toxicity in 24.4% (n=l01, 95% CI 20.4-28.55%) and lactic acidemia in 4.1 % (n=17, 95% CI 2.19, 6.03) of patients. Approximately, 13% (42/335) of patients experienced severe forms of these ADRs.

Lipodystrophy and lactic acidemia were the only two adverse reactions where the female patients were significantly more affected than their male counterparts (p<0.001 and p=0.047 respectively). Seventy nine percent (1071135) of female patients experienced lipodystrophy compared to 20.7% (28/135) of male patients. Exactly, 88.2% (15117) of female patients and 11.8 % (2117) of male patients experienced lactic acidemia (Table 2).

Factors associated with the medium to long term ADRs: When the data were adjusted for ARV regimens, bio-demographic factors, immunologic status and ADRs, there were no significant associations found between the occurrence of these ADRs with baseline weight, age and gender. Irrespective of the baseline regimen, data analysis showed slightly increased risk of experiencing the ADRs associated with increasing baseline CD4 cell count, HR 1.002 (95% CI 1.00-1.003, p=0.011).

After adjusting for bio-demographic factors, immunological and NRTI based regimens, single unmarried patients had a reduced risk of experiencing these ADRs (Hazard Ratio (HR) 0.66, 95% CI 0.45-0.97) compared to divorced patients, p=0.035. When the risk for these ADRs was assessed in patients on D4T and AZT as compared to other NRTIs, namely TDF and ABC, patients on D4T had a higher risk by 4.4 times (HR 4.42,95% CI 3.04-6.42, p<0.0001). On other hand, those on AZT based regimens had a 2.1 times higher risk of experiencing one of these ADRs (HR 2.11,95% CI 1.36-3.3; p<0.0001).

The risk of having any of these ADRs was also explored among patients on EFV, NVP and Lopinavirlritonavir (LPV/r) based regimens. The risk of developing these ADRs in patients on EFV based regimens compared to those on LPV/r was less by 86% (HR 0.14, 95% CI, 0.0530.37; p<0.0001), while the risk of ADR in among those using NVP based regimens was less by 46.6% compared with those on LPV/r (HR 0.53,95% CI 0.37-0.78; p=0.001).

DISCUSSION

The HIV infection is one of the specific factors that increase the risk of general adverse drug reactions

Table 2
Types of ADRs in Adult HAART Patients by Gender (n=261)

Occurrence of ADRs	n (%)	95% CI	Mean baseline CD4 cell count (95%CI) or (sd)	Female n (%)	Male N(%)	p-value
Overall	261	58.37-	131.5(120.1,141.9)	179	82	0.127
	(63.04)	67.71		(68.58)	(31.42)	
Anemia	3(0.72)		207.00(sd±128.57)	2(66.67)	1(33.33)	
CNS symptoms		3(0.72)	122.00(sd±148.35)	1(33.33)	2(66.67)	
GIT symptoms		7(1.69)	97.83(22.02,173.6)	5(71.43)	2(28.57)	
Hepatic	101	20.24,	120.4(103.2,137.6)	65(64.36)	36(35.64)	0.749
toxicity	(24.40)	28.55				
Lipodystrophy	135	28.07,	130.2(115.5,145.0)	107 (79.26)	28(20.74)	<0.001
	(32.61)	37.14				
Muscle pain	7(1.69)		109.71(40.7,178.7)	4(57.14)	3(42.86)	0.25
Peripheral	138	28.77,	125.3(110.4,140.3)	90(65.22)	48(34.78)	0.785
neuropathy	(33.33)	37.89				
Skin Reactions	15(3.62)	1.82, 5.43	172.3(122.8,221.8)	7(46.67)	8(55.33)	0.904
Lactic acidemia	17(4.11)	2.19,6.03	117.88(77.2,158.6)	15(88.24)	2(11.76)	0.047
Others	2(0.48)		138.00(sd±45.25)	0(0)	2(100.0)	

(7). Among the MDH adult HIV study subjects, 63% HIV positive study subjects on HAART experienced ADRs. Nearly (90%) all the HAART patients were commenced on D4T based regimens as per the national treatment guidelines that were in effect at the time of the study period.

Types of adverse drug reactions: A few of the more persistent or severe short term ADRs were recorded. The type of short term ADRS and the proportion of the affected areas of the body were as follows: central nervous system symptoms (0.7%), skin hypersensitivity rashes (3.6%), myopathy (1.5%), GIT symptoms (1.5%). As in other similar studies where D4T based regimens are predominantly used, the most common ADRs recorded were peripheral neuropathy (33%), lipodystrophy (33%), hepatic toxicity (24.4%) and lactic acidemia (4.1 %) (8-11). These are known toxicities of NR TIs over the medium to long-term and thought to be secondary to inhibition of mitochondrial DNA polymerase b (9). The four ADRs comprised 91.4% of all the incident ADR reactions and had an incidence rate of 49% per 100 person years.

Factors associated with medium to long term ADRs: Increasing age was the only bio-demographic factor found to be associated with occurrence of ADRs. For every additional year at baseline, the probability of experiencing medium to long term ADR increased 7.6%. This is consistent with literature and is possibly due to age-related alteration in pharmacokinetics and pharmacodynamics (12). Occurrence of ADRs was independent of gender, marital status, baseline CD4 cell count.

The female gender was not a significant risk factor to occurrence of ADRs collectively (p=0.127). This finding concurred with studies conducted by Johnson *et al* (13). More specifically, Menezes de Padua *et al* showed that there is a two-fold heightened ADR risk among the female gender to short term reactions that occurred before the fourth month of HAART, such as GI symptoms and allergy (14). This study demonstrated that occurrence of lipodystrophy (p<0.001) and lactic acidemia (p=0.047) were associated with the female gender. Similarly, Bonfanti *et al* demonstrated increased risk of lipodystrophy among the females (15). Furthermore, the higher risk of lactic acidosis in the female gender was demonstrated by Bonnet *et al*, Geddes *et al* and Boulassel *et al* (16-18). The increased propensity for NR TI -related adverse events in women may be related to higher levels of intercellular phosphorylation (19).

This study demonstrates that adult HIV positive patients on D4T and AZT based regimens had increased risk of experiencing ADRs compared to their counterparts on TDF or ABC based regimens by four and two times respectively. TDF is a much safer medicine than either D4T or AZT (20). This has been replicated in several settings and has led to recent guideline changes for HAART management internationally (20).

The risk of ADRs in adult HIV positive patients on EFV based regimens was less by 86% compared to patients on LPV/r based regimens (HR 0.14,95% CI, 0.053-0.37; p<0.0001). While the risk of ADR in those using NVP based regimens was less by 46.6% than for those on LPV/r (HR 0.53,95% CI 0.37-0.78; p=0.001). Based on these results, it appears as if EFV and NVP are safer than LPV/r. However, the patients on LPV/r were more likely to have been on HAART for longer and most probably were switched from NVP or EFV at one point in time. Additional study with adjustments for length of time on the individual ARVs may be needed to determine the true correlation between these medicines and risk of ADRs.

Despite the high frequency of ADRs among patients on HAART, the outcomes were favourable as there were no documented incidences of deaths or hospitalisations. In addition, a proportion of patients (44-59%) with medium to long term ADRs already had resolution of their reactions by end of the study period.

Limitations: First, this was a retrospective cohort study using routinely collected clinical data without independent real time confirmation of existence of adverse events or their outcome. However, this was minimised with the use of standardised patient clinical encounter forms based on the national protocols, designed to systematically collect information from clinical encounters. Non naive patients were also excluded from the study, because of increased likelihood of non availability of initial data.

Second, the ADRs documented in patient records were based on the clinical acumen of the clinicians, without independent laboratory and radiological confirmation of the existence of the event in the majority of cases. Variability was minimised by the use of standardised validated protocols. Lipodystrophy was the only ADR that would need additional case definition and validation to describe severity of the event. This has not yet been done by the world medical fraternity.

Third, it was not possible to study other factors, for lack of sufficient data, that could influence the occurrence of ADRs such as viral hepatitis, renal insufficiency, and alcohol consumption.

Despite these limitations and considering that this was a baseline study among the MDH HAART cohort, it is we believed that the findings are suitable and valid for informing programme and clinical management and comparing with other national, regional and global HAAR T cohorts studies.

In conclusion the ADRs that occurred frequently among HAART patients and were largely associated

with the medium to long term use of stavudine and nevirapine. Over a follow-up period of three and a half years approximately 63% of HIV infected patients on HAART presented with an ADR. Patients on D4T and AZT were significantly at higher risk of experiencing ADRs than their counterparts on TDF and ABC. In addition, increasing age at initiation of therapy was found to be the only bio-demographic risk factor. Despite the high frequency of ADRs there were no reported deaths or hospitalisations.

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