EVALUATING ADVERSE DRUG REACTIONS IN KWAZULU NATAL

Ms VK Manickum, B Pharm (UDW), M Pharm, (UKZN) BBA -cum laude (UNISA)
Dr F Suleman, B Pharm (UDW), M Pharm ((UDW), Phd (UIC,USA)

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

African Journal of AIDs Research 2012, 11 (2):75-81

Introduction

- South Africa is experiencing one of the most severe AIDs epidemics in the world.
- KwaZulu-Natal- has recorded the highest HIV prevalence rate of 39 % in 2008 to 40% among clinic attendants in 2009 (1)
- Antiretroviral Programme- initiated in KwaZulu-Natal in March 2004 at 4 accredited sites.
- As at the 30 April 2007, approximately 107000 patients were initiated at 75 sites within the province (2).
- Focus was on increasing access to HAART however insufficient attention given to medicine safety.

(1) Shisana, Rehle, Simbayi, Parker, Zuma, Bhana et al; Department of Health, 2010

(2) Mbanjwa, 2007

Introduction

Adverse drug reactions may

- Alter patient adherence to antiretroviral therapy,
- Decrease treatment efficacy
- Reducing treatment programme effectiveness and increasing the risk for emergence of secondary drug resistance.

Availability of numerous new drugs, fixed dose combinations and multi-source generic drugs makes it critical to monitor more systematically adverse events linked to Antiretrovirals.

Overview

- Spontaneous Reporting
- Solicited Reporting

Spontaneous Reporting

- Definition
- Unsolicited communication by health care professionals that describes one or more adverse drug reactions in a patient (Voluntary Process)

- Implemented from March 2004-April 2007

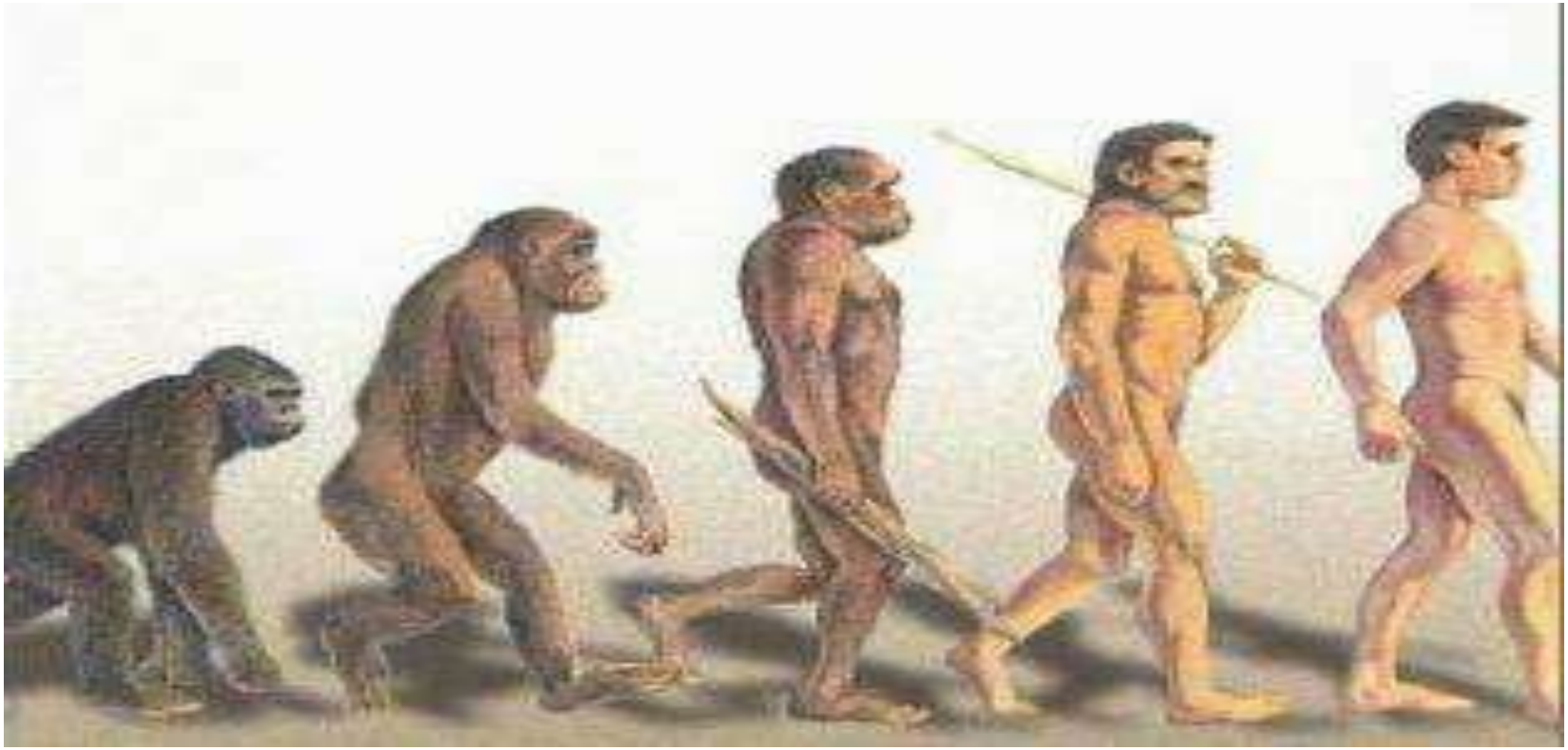
Spontaneous Reporting: Results

	1 March 2004-30 November 2004	1 December 2004-30 November 2005	1 December 2005-31 March 2007
Number of accredited Sites	31	55	63
Total number of patients initiated on HAART	4798	27027	64911
Number of sites that submitted reports (%)	0	1 (<2%)	21 (31%)
Number of valid adverse event reports received	0	49 (92%)	160 (37%)
Number of reports with insufficient information (%)	0	4 (7.5%)	270 (63%)
Total number of reports received	0	53	430

Limitations of Spontaneous Reporting System

- 1. Awareness
- 2. Training of Health Care Workers
- 3. Time Constraints
- 4. Causality unknown
- 5. Poor reporting of deaths/pregnancy exposures
- 6. Standardised adverse event reporting form

Evolution of Pharmacovigilance in KwaZulu-Natal



Spontaneous Reporting 2004-2007

Solicited Reporting 2007-current

Development of the Solicited System of Reporting

- Definition: The solicited system of reporting involved the mandatory reporting of adverse events on a solicited reporting form-when there was the need to change the regimen/antiretroviral drug , due to adverse events.
- Factors: Limited resources, the exponential increase in the numbers of patients on HAART.
- Implemented by KZN Pharmacovigilance Committee in May 2007.
- The solicited reporting forms were evaluated by pharmacists and consultants in accordance with case definitions.

Objectives

- Evaluate the frequency and types of adverse events reported through the solicited system of reporting.
- Determine whether the rate of reporting increased.
- Identify the regimens/antiretrovirals that were implicated in adverse drug reactions.
- Determine whether the demographic profiles of patients could be related to different adverse drug reactions.

Methodology

- **Study Design:** Retrospective audit
- **Study Period**: 1 May 2007-31 May 2008.
- **Study Setting:** Study conducted at Provincial Pharmaceutical Services; all public sector institutions were included.
- **Study Population:** Patients that were on HAART and experienced adverse drug reactions for which regimen changes were requested (n=3534).
- Patients that required non standard regimens (n=216).
- High risk patients who required post exposure prophylaxis (n=173).
- **Data Collection and Statistical Analysis**: Data was extracted from adverse event reports and entered on an excel spreadsheet. Data was analysed using SPSS v 15.0.

Methodology

- **Resources Required:**

-Human-Pharmacist at Provincial Offices, Clinical Consultants, Data Capturer, Healthcare workers at institutional level

-Physical: Functional facsimile machines.

-Informational: Guidelines and forms, training sessions

- **Study Variables:**

- Month of Receipt, hospital, gender of patient, age band, weight band, possible causative agent, antiretroviral regimen, use of concomitant medication, concomitant disease conditions, years on HAART when adverse drug event was diagnosed, adverse drug reaction that was experienced, the outcome and the reason for a change in regimen

- Ethical Clearance: UKZN and Department of Health Ethics Committee

Results

Demographic Characteristics of patients on HAART with adverse events

Variable	Total reports evaluated (n=3923) n%	Total on HAART (n=151276)
Gender:		
Female	2903 (74)	93088 (62)
Male	835 (21.3)	43232 (29)
Not Specified	183 (4.7)	14956 (9)
Patient Group:		
Adults	3651 (93.1)	
Paediatrics	89 (2.3)	
Not Specified	183 (4.7)	
Patients age group when regimens were changed		
0-14	98 (2.5)	
15-29	476 (12.1)	
30-44	1979 (20.4)	
45-59	688 (17.5)	
≥ 60	56 (16)	
Not Specified		
Average weight of the patients at the time a change of regimen was requested	65.65 kg (15.64)	
Pregnancy Status		
Not Pregnant	2783 (70.9)	
Pregnant	48 (1.2)	
Not Indicated	1092 (27.8)	

Results

Types of adverse drug reactions reported according to gender and age group

	Gender							
Adverse Drug Reaction	**Females (n=2408) n (%)**	**Males (n=638) n (%)**	**0-9 %**	**10-19 %**	**20-29 %**	**30-39 %**	**40-49 %**	**50-59 %**
Peripheral Neuropathy	532 (22.1)	289 (45.3	16.7	7.7	26.8	24.2	29.9	34.2
Symptomatic Hyperlactatemia	467 (19.4)	40 (6.3)	4.2	15.4	10.4	15.2	18.8	22.5
Gynaecomastia	13 (0.5)	99 (15.5)						
Lipodystrophy	448 (18.6)	49 (7.7)	33.3	42.3	23.5	19	10.8	8.5
Lactic Acidosis	278 (11.5)	19 (3)	4.2	0	7.9	9.8	11.2	10.6
Multiple Adverse Drug Reactions	550 (22.8)	103 (16.1	25	11.5	19.9	23	22.2	18.7
Other Adverse Drug Reactions	120 (5)	39 (6.1)	16.7	23	11.5	8.8	7.1	5.7

Results

1. Patients on

-Stavudine, Lamivudine and Efavirenz/Nevirapine were indicated as the current regimen in 3323 (84.7%) reports, (p value=0.000) when the adverse drug reactions were diagnosed.

--Medication for co-morbidities/opportunistic infections presented with a higher incidence (47.4%) of adverse events compare to patients on HAART only (44.3%) (p value<.005).

2. Stavudine was implicated as the possible causative agent in 2496 (93%) reports.

3. 2511 (64%) reports confirmed occurrence of adverse event within 0-1.75 yrs after HAART initiation.

Results

3. Single adverse events recorded in 2504 (63.8%) reports; multiple adverse events diagnosed in 683 (17.4%) reports.

4. Higher incidence of multiple adverse reactions (97.9%) recorded in patients on Stavudine, Lamivudine and Efavirenz/Nevirapine.

5. Relevant laboratory parameters recorded in 1019 (26%) reports. 291 (7.4%) reports did not display relevant parameters.

Results

6. Outcome indicated on reports

- Patient recovered-194 (4.9%)
- Patient not yet recovered-282 (7.2%)
- Died – 2 (.2%)
- Hospitalised-57 (1.5%)
- Regimen change-2826 (72%)

7. Zidovudine, Lamivudine and Efavirenz/Nevirapine was indicated as the proposed new regimen in 73.6% of reports

Adverse Drug Reaction Reported	**Possible Causative Agent**				
	(n= number of reports)				
Breast Disorders/ Reproductive System	**Stavudine (n=2946)**	**Efavirenz (n=110)**	**Zidovudine (n=46)**	**Nevirapine (n=25)**	**Other ARVs**
Erectile Dysfunction	0	1	0	0	0
Gynaecomastia	72	39	0	0	3
Pregnancy Exposure	1	5	0	0	0
Central Nervous System					
Convulsions	0	2	0	0	0
Depression	0	1	0	0	0
Drowsiness	0	8	0	0	0
Psychiatric Episodes	0	2	0	0	1
Hallucinations	0	6	0	0	0
Insomnia	0	4	0	0	0
Confusion	0	2	0	0	0
Dermatogical					
Skin Reactions	0	15	0	18	2
Haematological					
Anaemia	0	0	31	0	0
Neutropaenia	0	0	3	0	0
Red cell aplasia	0	0	0	0	1

Adverse Drug Reaction Reported	Possible Causative Agent				
	(n= number of reports)				
	Stavudine (n=2946)	**Efavirenz (n=110)**	**Zidovudine (n=46)**	**Nevirapine (n=25)**	**Other ARVs**
Hepatic					
Hepatitis/Transaminitis	6	5	0	3	2
Hepatic Steatosis	1	0	0	0	0
Pancreatitis	18	0	1	0	3
Metabolic	0	0	0	0	0
Lipodystrophy	494	10	1	0	7
Lactic Acidosis	304	0	1	0	2
Symptomatic hyperlactatemia	529	0	2	0	1
Multiple Organ Systems					
Multiple adverse drug reactions	655	8	7	4	11
Neurological					
Peripheral Neuropathy	866		0	0	4
Other:	0	0	0	0	2
Diarrhoea	0	0	0	0	2
	0		0	0	0

Findings

- 1. Female patients are more susceptible to symptomatic hyperlactatemia, lipodystrophy, lactic acidosis, and multiple adverse drug reactions in comparison to male patients in KwaZulu-Natal. Male patients are at a higher risk of peripheral neuropathy and gynaecomastia.

- 2. Peripheral neuropathy, symptomatic hyperlactatemia, lactic acidosis and multiple adverse drug reactions were more prevalent in the age band 20-59.99 years. A higher incidence of lipodystrophy was detected in patients within the age band 0-19.99 years.

Findings

- 3. Patients that were on Stavudine containing regimens presented with a higher incidence of peripheral neuropathy, symptomatic hyperlactatemia, lipodystrophy, lactic acidosis and multiple adverse drug reactions, compare to patients on other regimens.

- 4. Patients that were on medication for co-morbidities/opportunistic infections had an increased incidence of adverse drug reactions in comparison to patients on HAART only.

Findings

- 5. Patients on Stavudine containing regimens had a risk of developing lipodystrophy, peripheral neuropathy, symptomatic hyperlactatemia and lactic acidosis within an average time period of 0.643, 0.885, 0.883, and 0.966 years respectively.

Limitations

- The physical and biochemical effects of HIV on the different organ systems were not considered when confirming the occurrence of the adverse drug event.

- Co-morbidities and treatment for co-morbidities/over the counter/ supplementary/traditional medication were not indicated on the forms, as adverse drug reactions were directly attributed to HAART. Therefore incomplete information was assessed, when establishing causality.

- Only adverse reactions that warranted a change in regimen were recorded and reported. This resulted in non serious adverse drug reactions not being reported.

Limitations

- Deaths and pregnancy exposures were not/poorly reported.

- Limited numbers of doctors, pharmacists and nurses in KwaZulu-Natal and the high burden of patients at facilities, clinicians did not have time to complete forms. In addition relevant clinical/laboratory information may have not been present in patients file.

- This system did not allow for the calculation of rates. The total population that was receiving HAART was not accurate, as the births, deaths and migrations were not being recorded. This eliminated a precise denominator to calculate mortality rates.

Outcome of Solicited Reporting System

- Outcome of Solicited reporting system-3923 completed reports received from 1 May 2007-31 May 2008 in comparison to 63 % incomplete reports received from March 2004-2007

- Implementation: Improved the frequency and the completeness of adverse drug reaction reporting associated with HAART.

- Provided signals for policy makers

Impact: Poor Pharmacovigilance Systems

Adverse Events

Poor Adherence

Traditional/ Supplementary Medicines

Socio-Economic Factors

HIV drugs failing in Africa

ARVs: Researchers warn of spreading resistance

KERRY CULLINAN

Uganda was one of the

Conclusion

- HAART significantly reduced mortality and morbidity in HIV positive patients, adverse drug reactions are prevalent.
- Role of healthcare worker to identify, correctly record and report adverse events.
- Result: Data collation and analysis, policy makers able to make evidence based decisions regarding improving the quality of clinical care.
- Solicited system of reporting can be incorporated into a systematic risk assessment system in a resource constrained environment for the monitoring and evaluating of adverse events.

Acknowledgements

- Department of Health: KwaZulu-Natal
- MSH/SPS
- Prescribers and Clinicians in KwaZulu-Natal
- Mr CB Shabalala


MCHUMOR.COM by T. McCracken
"It appears to be some sort of reaction
o your herbal pain medication."

- THANK YOU