British Journal of Pharmaceutical Research
4(6): 714-721, 2014

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Adverse Drug Reaction Reports in an Antiretroviral Treatment Centre in Jos, North Central Nigeria

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Authors' contributions

All the authors collaborated in carrying out this work. Authors LOO, VBO, IOA and KDF designed the study, did the literature search, data analysis and drafted the manuscript. Authors IAL, NN, CD and AIF did the data acquisition and critically reviewed the manuscript. Authors PA and OAA defined concepts and intellectual content and critically reviewed and edited the manuscript for publication. All authors read and approved the final manuscript submitted for publication.

Original Research Article

Received 23 August 2013
Accepted 14th December 2013
Published 30th January 2014

ABSTRACT

Background: Reports of adverse drug reactions (ADR) in the era of increasing uptake of antiretroviral drugs particularly in Sub Saharan Africa and especially in Nigeria have been on the rise.
Aim: We set out to collate and characterize the pattern of adverse drug reactions in patients on antiretroviral drugs in our treatment centre.
Study Design: Retrospective Cross sectional study
Place and Duration of Study: The study was carried out at the APIN Centre, Jos University Teaching Hospital, Plateau State, North Central Nigeria from July 2010 to December 2012.
Methodology: We reviewed the case files and data base entries of 215 patients attending our treatment centre. These are patients who had reported cases of adverse drug

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reactions. We took note of demographic profiles of the patients, the medical history as well as the different types of antiretroviral drugs the patients were taking. The types of adverse drug reactions and offending drugs were noted and categorized using descriptive statistics.

Results: Out of 215 case files and databases of patients in which there were reports of adverse drug reactions, 80 (37.2%) were male and 135 (62.8%) were female. Almost thirty two percent (31.6%) of the patients were on Zidovudine/Lamivudine/Nevirapine (AZT/3TC/NVP), 14.9%on Zidovudine/Lamivudine/Tenofovir/Lopinavir/ritonavir (AZT/3TC/TDF/LPV/r), 13.5% on Stavudine/Lamivudine/Nevirapine (D4T/3TC/NVP). Anemia was the most common ADR representing 23.4% of all ADRs and 29.3% of all ADRs were associated with Zidovudine.

Conclusion: Our study shows that in antiretroviral treatment centre such as our own, healthcare providers/practitioners should take particular note of troubling adverse drug reactions such as anaemia. Healthcare providers/practitioners should particularly have in place alternative treatment regimens as these adverse drug reactions may be potential cause of medication non adherence which in the long run lead to treatment failure.

Keywords: Antiretroviral drug; adverse drug reactions; drug therapy; side effect.

1. INTRODUCTION

In the more than three decades since the Human Immunodeficiency Virus (HIV) was first characterized, the epidemic has continued to be a deadly scourge of human kind. As at 2010, Joint United Nations program on AIDS (UNAIDS) estimates that close to 33.2 million people are living with the disease worldwide; with a corresponding high number of deaths associated with the Acquired Immunodeficiency Syndrome (AIDS) [1]. The introduction of antiretroviral drugs (ARVs) and especially the Highly Active Antiretroviral therapy (HAART) has been somewhat revolutionary, transforming the infection from a fulminant and deadly disease in some cases to a long term manageable chronic disease. This is due mainly to concerted efforts being put in place by developed countries and international organizations to mitigate the impact of the disease in a significant way worldwide and especially in the resource constrained countries. As a result of these efforts, access to ARVs have become easy with many eligible people living with HIV/AIDS able to obtain the much needed life saving drugs [2] leading to substantial decreases in morbidity and related mortality. In fact, it has been estimated that in this era of HAART, it is possible for a 20 year old person newly infected with HIV to live at least an additional 50 years which is very close to a normal life expectancy [3].

Even though appreciable progress has been made in control of the pandemic and in the treatment care and support for people living with HIV and AIDS, the preponderance of unwanted effects, side effects, adverse drug events, adverse drug reactions and/or toxicities have tended to be a major drawback to the use of ARVs. This is not really different from the experience with many other chronic diseases for which drugs are administered for a prolonged period of time.

Adverse drug reactions may represent a spectrum ranging from mild noxious, unintended responses to a medicine to those reactions that are serious, life threatening and/or even fatal [4]. The adverse drug reaction problem is therefore a serious limitation to the use of ARVs. This is more so because for successful treatment, there is need to take these agents daily for

a prolonged period of time taking into cognizance the fact that antiretroviral therapy (ART) will continue to be the mainstay of the global response to HIV [3].

Adverse reactions represent just one set of problems encountered with ARVs. Depending on the class of ARV and the treatment regimen involved, these adverse drug reactions may range from fatigue to nausea, mild to moderate and severe rashes to long term metabolic complications such as diabetes mellitus, hyperlipidemia and abnormal fat distribution and peripheral neuropathy [5]. Many of these adverse reactions are identified in the review by Max and Sherer [6]. Eluwa et al. [2] recently cited reports that indicate incidences of adverse drug reactions in patients on ARVs to range from 11 to 35.9% and may sometimes even reach up to 54%.

The high incidence rates reported means that particular attention needs to be given to the issues of adverse drug reactions. This is because Adherence to ART is an important predictor of treatment efficacy. It is also of first importance to note that even though many other factors may interfere with proper adherence to ART, adverse reactions are among the most important [7,8].

Adverse drug reactions or adverse drug events are commonly encountered with all available antiretroviral agents. It is therefore important to anticipate, recognize, and manage them when providing primary care for HIV-infected patients if there is to be treatment success [6]. In Nigeria and indeed in many other resource constrained countries especially in sub-Saharan Africa, there is an aggressive roll out of antiretroviral treatment centers. There is need therefore to properly understand associated adverse reactions to ARVs. We set out to collate and characterize the incidences of adverse drug reactions in patients on antiretroviral drugs in our treatment centre. This is with a view to providing information that will help in putting in place treatment strategies that will guarantee treatment success.

2. METHODOLOGY

2.1 Study Design

This is a Retrospective Cross sectional study of documented adverse events.

2.1.1 Study site

The study was conducted at APIN Center, Jos University Teaching Hospital, Jos, Nigeria. The site is a PEPFAR program founded in 2004. The clinic provides ambulatory HIV/AIDS care, treatment and support to over 9000 patients, an average of 250 patients are attended to daily. The clinic runs from Monday – Friday.

2.1.2 Study population and sample size

All adult patients above 18 years on ART who had documented reports of ADR between July 2010 and December 2012 at APIN Center, Jos University Teaching Hospital were analyzed. The total number of such patients was 215.These patients were initiated on combination antiretroviral therapy consisting of various ART regimens.

2.2 Data Collection

Socio-demographic and clinical information of patients including age, sex, weight, type of HAART regimen, reported ADR, implicated drug(s) and severity of ADR were extracted from toxicity and pharmacy data in the FileMaker Pro software version 10.5 designed by President and Fellows of Harvard College, Harvard School of Public Health, and transferred to an excel spread sheet. Reports of ADRs based on patient's complaints and/or morphological changes as noticed by pharmacists, physicians or nurses during routine drug pick-ups as well as those revealed by laboratory investigations are documented by the clinicians using the toxicity and National Agency for Foods, Drug Administration and Control (NAFDAC) pharmacovigilance forms which was later transferred to the toxicity data-base. Drug information charts [9] provided by the President and Fellows of Harvard College, Harvard School of Public Health provided a ready guide as to the class toxicities of antiretroviral drugs as well as the specific ADR attributable to a particular antiretroviral drug. These drug information charts are made readily available at the patient triaging table, physician consulting rooms, pharmacy drug dispensing rooms and the laboratories. The ADRs were classified using descriptive statistics based on the affected organ systems, namely, metabolic/endocrine system, cardiovascular/respiratory system, central/peripheral nervous system, skin and appendages, gastrointestinal/hepatobiliary and renal system.

3. RESULTS

Of the 215 patients that reported ADRs 81 (37.7%) were male and 134 (62.3%) were female. The mean age for all patients were 42±10.4 years and mean weight was 61±13.8 kg. The percentage of patients on different ART treatment regimens, the drugs associated with different ADRs as well as the percentage occurrence of the different ADRs are presented in Tables 1, 2 and 3 respectively.

Table 1. ART treatment regimens and the number of patients on them (n= 215)

Regimen	Frequency	Percentage
Zidovudine/Lamivudine/Nevirapine (AZT/3TC/NVP)	68	31.6
Zidovudine/Lamivudine/Tenofovir/Lopinavir/ritonavir (AZT/3TC/TDF/LPV/r)	32	14.9
Stavudine/Lamivudine/Nevirapine (D4T/3TC/NVP)	29	13.5
Tenofovir/Emtricitabine/Efavirenz (TDF/FTC/EFV)	27	12.6
Tenofovir /Lamivudine/Nevirapine (TDF/3TC/NVP)	17	7.9
Zidovudine/Lamivudine/ Efavirenz (AZT/3TC/EFV)	13	6
Zidovudine/Lamivudine/Tenofovir/Atazanavir/ ritonavir (AZT/3TC/TDF/ATV/r)	9	4.2
Tenofovir /Lamivudine/Efavirenz (TDF/3TC/EFV)	8	3.7
Zidovudine/Lamivudine/ Lopinavir/ritonavir (AZT/3TC/LPV/r)	3	1.4
Tenofovir /Lamivudine/ Lopinavir/ritonavir (TDF/3TC/LPV/r)	2	0.01
Stavudine/Lamivudine/ Efavirenz (D4T/3TC/EFV)	1	0.005
Zidovudine/Lamivudine/ Tenofovir (AZT/3TC/TDF)	1	0.005
Tenofovir/Emtricitabine/Nevirapine (TDF/FTC/NVP)	1	0.005
Stavudine /Tenofovir /Lamivudine (D4T/TDF/3TC)	1	0.005
Abacavir/Lamivudine/ Efavirenz (ABC/3TC/EFV)	1	0.005
Zidovudine/Lamivudine/ Atazanavir/ritonavir (AZT/3TC/ATV/r)	1	0.005
Lamivudine/Darunavir/Raltegravir/ritonavir (3TC/DRV/RAL/r)	1	0.005

Table 2. Associated drug and percentage of ADR

Drug	Percentage of ADR
Zidovudine	29.3
Nevirapine	20.5
Efavirenz	18.1
Stavudine	13.5
Lopinavir	10
Tenofovir	6
Atazanavir	0.02
Emtricitabine	0.01
Darunavir	0.01
Abacavir	0.01

Table 3. ADRs and percentage occurrence (n= 215)

ADR	Frequency	Percentage of ADR
Anaemia	50	23.4
Skin rash/Stevens Johnson Syndrome	34	15.9
Lipodystrophy	34	15.9
Central Nervous System effects	29	13.6
Jaundice/Hepatotoxicity	16	7.5
Diarrhoea	16	7.5
Renal cases	10	4.7
Gynaecomastia	7	3.3
Body pain/Fatigue/Malaise	5	2.3
Discoloration of nails/hyperpigmentation	5	2.3
Peripheral neuropathy	4	1.9
Vomitting/Nausea	3	1.4
Ascites	1	0.5

4. DISCUSSION

We observed that more females reported ADRs than males just as in a similar report in Nigeria [2].This is not surprising because there is increasing realization of the fact that sex differences may exist in several aspects of HIV infection and its management. These may include differences in the susceptibility to ADRs as well as tolerability of some antiretroviral drugs [10]. But even as the reasons for these differences have largely remained unclear [11], emerging evidence suggests that women may be at increased risk of developing adverse effects of antiretroviral drugs. Several mechanisms have been proposed to explain these sex differences in drug effects. Some of these include physiologic differences between men and women and influences of sex hormones on drug metabolism [12].

Anaemia a known side effect or ADR of zidovudine [13] has the highest percentage of all ADRs we encountered. This is not surprising because close to 60% of the different ART treatment regimens as can be seen in Table 1 contain zidovudine in combination with other antiretroviral drugs. The implication of this as highlighted in other reports [6] is that for these patients, the haemoglobin and haematocrit levels should be closely monitored. In effect, facilities should be in place to make this possible. Still from Table 1, 53% of our patients are on a nevirapine based regimen and 20.5% of all reported ADRs were attributable to

nevirapine. This could include issues such as jaundice and liver toxicities, skin rashes and Stevens Johnson Syndrome. As a result of some of these effects, treatment protocols that involve nevirapine as part of an ART regimen recommend that nevirapine dose be reduced for the first 14 days of therapy. Lipodystrophy represented 15.9% of all ADRs encountered. This is better understood when cognizance is taken of the fact that lipodystrophy is mainly associated with stavudine. Because of this peculiar and troubling side effect as well as peripheral neuropathy and other toxicities, stavudine was withdrawn from our ART regimens in early 2010. Even then, lipodystrophy and other complications such as lactic acidosis are associated with many nucleoside reverse transcriptase inhibitors [14]. Central nervous system side effects represented 13.6% of all reported ADRs. These are effects attributable to efavirenz [15] and from Table 2; the percentage of ADRs attributable to the drug is 18.1%. More than 20% of our patients are on one regimen or the other containing efavirenz.

Ten percent of the ADRs are attributable to lopinavir in conjunction with ritonavir even as more than 16% of our patients are on a regimen which contains the drug. The main adverse effect associated with it in our patients relates mainly to gastrointestinal system effects such as diarrhoea. As a result of this and other effects associated with lopinavir and ritonavir such as fat maldistribution, hyperglycaemia, increased transaminase levels [16], we are beginning to transition to protease inhibitors such as atanazavir and ritonavir. This is in view of literature sources showing that atanazavir and ritonavir have better pharmacokinetic and pharmacodynamic properties as well as fewer ADRs than lopinavir and ritonavir [17] and our results support this. Of the close to five percent of our patients on an atazanavir based regimen so far, less than 0.5% of the ADRs are attributable to atazanavir. Similarly, darunavir, the other protease inhibitor now used in our facility appears to have minimal side effect.

In the drug management of HIV/AIDS, great care and attention needs to be given to the issue of ADRs. This is because ADRs and other side effects play a major role in the success or otherwise of treatment. Side effects and ADRs could among other things be responsible for medication non adherence [6,18] and ultimately treatment failure. Furthermore in the face of limited resources, any issues that may compromise adherence and contribute to treatment failure should be avoided. A limitation to our study is the possibility that the CNS effects attributable to efavirenz may have been due to drug interaction or patient lifestyle which our study did not control for. Also, as this was a retrospective study, it was difficult to verify already documented information.

5. CONCLUSION

ADRs negatively affect the outcomes of drug therapy. It is important that in disease conditions such as HIV/AIDS where drugs are to be taken for a prolonged period of time, care givers need to be conversant with adverse drug reactions that are to be expected in the treatment area. This will help in putting in place treatment strategies that will reduce or ameliorate these with a view to improving medication adherence, preventing treatment failure and wastage of other resources; as well as preserving future treatment options.

ETHICAL APPROVAL AND PATIENT CONSENT

This study was approved by the ethics committee of the Jos University teaching hospital, Jos and the institutional review board of the Harvard school of public health, Boston, MA, USA. All patients signed a written informed consent.

FUNDING

APIN JUTH is funded in part by the US Department of health and Human Services, Health Resources and Services Administration (U51HA02522) and CDC through APIN (PS 001058).The contents are solely the responsibility of the authors and do not represent the official views of the funding institutions.

ACKNOWLEDGEMENTS

We appreciate the support of management and staff of APIN centre JUTH Jos.

COMPETING INTERESTS

All authors declare that there is no conflict of competing interests.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=407&id=14&aid=3486