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Prevalence and Extent of Adverse Drug Reactions in Sudanese Patients in Highly Active Anti-retroviral Therapy Regimens

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Abstract

Objective: To assess the prevalence and extent of Adverse Drug Reactions (ADRs) associated with the use of Highly Active Antiretroviral Therapy (HAART) among the Sudanese HIV/AIDS patients.

Design: Prospective spontaneous reporting of Adverse Drug Reactions with specially designed HIV/AIDS specific Adverse Reactions case report form

Setting: HIV/AIDS Voluntary Counseling and Testing Center (VCT) at University affiliated tertiary care center.

Population and sample: Participants were HIV infected adult patients in HAART regimens; recruited at HIV/AIDS public referral center (VCT) during the period of the study.

Results: Among the 257 patients recruited, 166 (64.5%) received their HAART regimens regularly. At least one adverse reaction was reported by health care professional as a result of one of the three HAART regimens, leading to an incidence rate of (0.44). Overall, 226 adverse reactions were registered, with epidermal necrolysis and dermatological adverse effects (15.5%), gastrointestinal adverse effects (15%) and peripheral neuropathy (14.2%) being the most common ones. TB and HIV/AIDS Co-infection presents in (33.8%) of patients. There were 24 patients that recorded hospitalized and one record of death due to the adverse reactions; which could not be confirmed or rolled out. Among the 74 patients experiencing the adverse reactions; (75.7%) of the patients were treated from the symptoms of adverse reactions with other medicines and 18 patients (24.3%) had their HAART regimen switched to at least one or another different regimen.

Conclusion: Despite the limitations and observations of this study, and considering this to be the first study on adverse reaction among patients initiating HAART in Sudan, we believe our findings from this study are suitable and valid for comparison purposes within our Sudan national AIDS program.

Introduction

Generally the data on adverse reactions to drugs treatment have been recorded in clinical trials, post-marketing analyses and anecdotal reports; however such data are available only in well developed countries and it might not be an up-to-date. The Thalidomide tragedy around 1962 which resulted in the birth of more than 10,000 malformed children by women who took the drug at the early stage of pregnancy had led to greater attention and focus, both nationally and internationally, on drug safety issues [1]. Then, the sixteenth World Health Assembly on 1963 highlighted the urgent need for action to rapid dissemination of information on Adverse Drug Reactions (ADRs), led to the World Health Organization (WHO) International Drug Monitoring Project in 1968. At the same time, spontaneous systems for the reporting of adverse drug reactions (ADRs) were established in some well developed countries. The major purposes of these systems are to detect unknown or poorly understood adverse effects of medicines [2, 3].

Pharmacovigilance and Spontaneous reporting of (ADRs)

From these beginnings, emerged the practice and science of Post Marketing Surveillance (PMS) and Pharmacovigilance. The WHO defines Pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of ADRs or any other possible drug related problems (4, 5). The aims of Pharmacovigilance according to WHO are:

• Improve patient care and safety in relation to the use of medicines,

• Improve public health and safety in relation to the use of medicines,

• Contribute to the assessment of benefits, harm, effectiveness and risk of medicines and encourage their safe, rational and more effective use, and

• Promote understanding, education and clinical training in Pharmacovigilance and its effective communication to the public (WHO, 2002)[5].

In Sudan, pharmacovigilance is still in its infancy steps and it is yet to gain the momentum needed to cope with the demands of a country that is already under the pressure of war, instability and high disease burden. A major step in this direction was the establishment of national pharmacovigilance center in February 2006. It was concerned with assuring the safety of circulating medicines in the Sudanese market in accordance with the global trend in the containment of counterfeit medicines danger.

Sudan Pharmacovigilance department is now a full member of the (WHO) collaborating center for international drug monitoring program which is based in Uppsala Sweden, and known as Uppsala Monitoring Center (UMC)[6,7].

Although the value of the spontaneous reporting system of ADRs has been repeatedly proven, unfortunately serious suspected ADRs are only reported in 5-15% of all incident cases [8]. Thus the usefulness of the spontaneous reporting system is impaired, as too few physicians report and much less (ADRs) than actually occur are notified.

Generally about 6% of all hospital admissions to medical wards have been shown to be due to ADRs [9], and fatal ADRs rank among the most common causes of death in the United States [10, 14]. The economic burden of ADRs is considerable also; the estimated direct costs of ADR-related hospital admissions in the United States are well above $47 billion annually [11]

Thus there are many reasons, from the wellbeing of the patients to the economical use of the available resources, to identify ADRs for every drug as early as possible and to prevent them, as much as possible.

Adverse drug reactions

Adverse drug reaction is defined as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product." Such reactions are currently reported by use of WHO's Adverse Reaction Terminology, which will eventually become a subset of the International Classification of Diseases [1].

Adverse drug reactions are classified into six types (with mnemonics) [12, 13]:

- Dose-related (Augmented),
- Non-dose-related (Bizarre),
- Dose-related and time-related (Chronic),
- Time-related (Delayed),
- Withdrawal (End of use), and
- Failure of therapy (Failure).

Timing, the pattern of illness, the results of investigations, and rechallenge can help attribute causality to a suspected ADRs. Management includes withdrawal of the drug if possible and specific treatment of its effects. Suspected ADRs should be reported and well-developed surveillance methods can detect reactions and prove associations.

Human immune deficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS)

Aepidemiology: HIV, the cause of the acquired immune deficiency syndrome (AIDS), continues to spread, being described as a global health emergency by the World Health Organization (WHO) in 2003. UNAIDS estimates for 2002 are that 41 million people are infected with HIV world-wide, over 70% of them are in sub-Saharan Africa. Approximately 16000 new infections occur daily, the majority are in young adults. HIV is now the leading single cause of death in adults, causing 5 million deaths in 2003. In sub-Saharan Africa 5000 men and women and 1000 children die of HIV every 24 hours. Dramatic rises in infection have been seen in SE Asia with Eastern Europe and Russia having the most rapidly expanding epidemic in 2003[16].

The human and economic costs are huge - 33% of 15-year-olds in high-prevalence countries in Africa will die of HIV, life expectancy in African countries is falling with an inevitable impact on the fabric of society and on economic growth and stability [17]. The advent of more effective therapy for HIV has brought geographical differences in the impact of the epidemic into stark relief, with falling mortality and morbidity in resource-rich settings that are unmatched in poorer parts of the world. Although in the UK and other wealthy countries deaths from HIV have fallen, new diagnoses are rising sharply [16, 27]. At least 5000 new diagnoses were recorded in the UK in 2003, a 20% increase over the preceding year, and the highest annual number since surveillance began, with the result that prevalence is raising. Demographics have varied greatly within different regions influenced by social, behavioral, cultural and political factors. Despite the fact that HIV can be isolated from a wide range of body fluids and tissues, the majority of infections are transmitted via semen, cervical secretions and blood. The character of the epidemic in different regions of the world has been influenced by the relative frequency of each of the routes of transmission [16, 17].

Sudan is geographically located among neighboring countries with higher HIV prevalence ranging between 4-13%. The HIV prevalence in Sudan is estimated at 2.6%, the highest in the EMRO region and expected to rise. Sudan national HIV/AIDS control programs (SNAP) depends mainly on donor agencies for funding and capacity building. And all drugs for HIV/AIDS are provided by the Global fund for AIDS [16, 18, 19].

Treatment of HIV/AIDS

Highly Active Anti- Retroviral Therapy (HAART) is the name given to aggressive treatment regimens used to suppress HIV viral replication and the progression of HIV/AIDS disease. The usual

HAART regimen combines three or more different drugs such as two nucleoside reverse transcriptase inhibitors (NRTIs) and a protease inhibitor (PI), two NRTIs and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or other such combinations. These treatment regimens have proven to reduce the amount of active virus and in some cases can lower the number of active virus to the limits that are undetectable by current blood testing techniques (16).

HAART has, without doubt, changed the lives and the course of the disease in those HIV infected people. Since the "HitEarly, Hit Hard" triple-therapy concept was first introduced in 1995, there has been a striking reduction in AIDS deaths in those HIV-infected individuals who can avail themselves of treatment [16, 18]. HAART treatment is four-folds potent than other antiretroviral treatments. However, it is very complex and it may cause serious ADRs and (potentially lethal) side-effects or drug interactions which pose difficulty with compliance, often entail large numbers of pills with frequent dosing, and carry serious potential consequences from the development of viral resistance [16, 18].

Classification of HAART

All HAART target enzymes, which are important for HIV RNA replication functioning. Currently available antiretroviral therapies for HIV infected person (ARVs) are belong to two major classes of drugs (according to their mode of action):

Reverse transcriptase inhibitors (RTIS)

These inhibit the enzyme that converts the viral RNA genome into a DNA copy. It is further divided into:

• Nucleoside reverse transcriptase inhibitors (NRTIs) which include: Abacavir, Adefovir Dipivoxil, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir, Zalcitabine and Zidovudine

• Non-nucleoside reverse transcriptase inhibitors (NNRTIs) which include: Efavirenz and Nevirapine

Protease inhibitors (PIS)

Those inhibit the viral enzyme, which contributes to the viral protein processing. It include: Amprenavir, Atazanavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir and Saquinavir.

Both physicians and patients should consider the advantages and disadvantages of the HAART before starting the treatment, the advantages include controlling of viral replication, improve patient's quality of life and increase the lifespan. While the disadvantages of the HAART may include the annoying side effects or sever adverse reactions, drug resistance which may limit the treatment options in the future and increase the risk of transmission of resistant strains.

Significant HAART associated adverse reactions

The development of highly effective antiretroviral drugs over the last few decades has brought remarkable benefits for the patients suffering from HIV/AIDS. The other side of the coin is that ADRs occurs. Unfortunately, up to 25% of all HIV/AIDS patients discontinue their initial HAART regimen because of treatment failure, toxic effects or noncompliance within the first eight months of therapy. Several strategies have been implemented to improve treatment duration (20, 21).

Antiretroviral therapy can cause a wide range of ADRs, some are common and mild which occurring early in most antiretroviral regimens and that include gastrointestinal effects such as bloating, nausea and diarrhea, which may be transient or may persist throughout therapy [22]. Other common nuisance adverse effects are fatigue and headache caused by AZT (Zidovudine) and nightmares associated with EFV (Efavirenz). Several uncommon but more serious adverse effects associated with antiretroviral therapy, including AZT associated anemia, d4T (Stavudine) associated peripheral neuropathy, PI-associated retinoid toxicity and NNRTI-associated hypersensitivity reactions, and they are treated according to accepted therapy for these conditions in patients not receiving HAART [23]. However, the other subtle and serious adverse reactions are lactic acidosis, hepatic steatosis, hyperlactatemia, hepatotoxicity, hyperglycemia, fat maldistribution, hyperlipidemia, bleeding disorders, osteoporosis and skin rash.

The risk of specific side effects and/or adverse reactions varies from drug to drug, from drug class to drug class, and from patient to patient. A better understanding of the adverse effects of antiretroviral agents is of great interest for both; the health care team who care for HIV positive patients and also for the patients who are in HAART regimen.

There is a poor record of reporting ADRs in hospitals worldwide [24, 26, 28]. Thus, the opinions and attitudes of hospital physicians in the problem of spontaneous reporting of ADRs and the ways to solve them are very important.

Due to the ongoing development of new antiretroviral agents, prompt understanding and management of ADRs become very important to improve treatment duration. The sustained benefits of the HAART have led to far greater number of ADRs among patients receiving at least three drugs for greater periods of time [25, 29, 30]. Moreover, drug-related toxicity is being increasingly recognized because of the declining incidence of HIV associated opportunistic infection.

Aim and objectives

The aim of this study is to assess the prevalence and extent of adverse drug reactions associated with the HAART treatment among the Sudanese patient and to help the health care professionals in Sudan to gain a working knowledge of the adverse reactions associated with the use of HAART, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment, promoting the early recognition and reversal of potentially serious adverse effects, and reducing the potential for adverse drug interactions.

The objectives of this study are

To determine the type of adverse drug reactions in Sudanese HIV/AIDS infected patients in HAART.

• To quantify the extent of the prevalence of adverse drug reactions among the Sudanese HIV/AIDS patients undergoing HAART treatment.

• To assist physicians to understand the purpose of spontaneous reporting of adverse drug reactions and stimulate their reporting attitude.

• To identify the most common short and long term toxicity and adverse reactions associated with the HAART treatment in Sudanese patients.

• To specify the factors that influences the occurrence of adverse drug reactions in the Sudanese patient treated with HAART.

• Eventually, to help physicians gain a working knowledge of these adverse reactions, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment, promoting the early recognition and reversal of potentially serious adverse reactions, and reducing the potential for adverse drug interactions.

• To generate sufficient number of ADRs reports which can be used by the Sudan pharmacovigilance program to maintain their membership at the WHO International Drug Monitoring Program

• To make recommendations to reduce the incidence of adverse drug reactions associated with HAART treatment in the Sudanese HIV/AIDS positive persons and to enhance the current practice of reporting the adverse drug reactions.

Literature review

In contrast to the first decade of the AIDS epidemic, the past decade has seen an increasing separation between AIDS care and palliative care services. While this may be due in part to the perception that AIDS is no longer a uniformly fatal illness, AIDS in fact remains an important cause of morbidity and mortality for young adult populations worldwide, particularly among certain racial-ethnic minorities. And since introduction of HAART; AIDS has been transformed into a more manageable, chronic disease, nevertheless the opportunities for adverse reactions has been increased in the presence of this large number of combinations therefore patients with AIDS continue to experience a high burden of adverse reactions and other chronic symptoms over a longer period of time, with a disease course marked by more cumulative exacerbations and remissions. Advance care planning and discussions of goals of care are more complex and involve more uncertainty than was the case when prognosis was clear-cut and treatment options were more limited [21].

The introduction of HAART has led to a significant reduction in AIDS-related morbidity and mortality[1,3].Recent studies shown that up to 25% of patients discontinue their initial HAART regimen because of treatment failure (inability to suppress HIV viral replication to below the current limit of detection, 50 copies/ml), toxic effects or noncompliance within the first 8 months of therapy.[4,5] Several strategies have been implemented to improve treatment duration[31].While development of new antiretroviral agents continues, efforts to maximize the effectiveness of currently available treatments include attempts to better understand and manage adverse effects. Each antiretroviral medication is associated with its own specific ADRs or may cause problems only in particular circumstances [21, 32]. Similarly, class specific adverse effects may occur. One of the drug classes used in HAART is the nucleoside reverse transcriptase inhibitors (NRTIs), which commonly form the "backbone" of the antiretroviral cocktail; this class includes zidovudine (AZT), lamivudine, didanosine (ddI), stavudine (d4T), abacavir (ABC) and the newly released nucleotide analogue tenofovir. Two NRTIs are often combined with 1 medication from either of the 2 remaining classes, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the protease inhibitors (PIs)[31, 33]. The NNRTI class comprises nevirapine (NVP), delavirdine (DLV) and Efavirenz (EFV).

Studies conducted primarily in developed countries have shown that ADRs are a significant cause of hospital admission, prolong hospital stay and consequently increase the cost of disease management in patients [34]. A large proportion of these ADRs have been shown to be preventable through improved drug prescribing, administration and monitoring for adverse effects [33, 34].

HAART use has significantly changed the pattern of morbidity and mortality among HIV-infected patients [31, 33-37].However, such benefits can only be achieved with high levels of adherence. Among several factors, the influence of adverse reactions to ARV on therapy discontinuation and non-adherence has been widely documented in observational studies [38, 43]. Adverse reactions have been described as single symptoms (e.g., nausea, headache, anemia), or as symptoms involving organs or systems (e.g., gastrointestinal, hematological reactions), classified according to severity or intensity, or estimated using scales or absolute numbers [44, 45]. Additionally, medical charts and interviews with patients represent the most commonly used sources of information in such studies [37, 38, 41, 44, 46, 47].

It is known that the incidence of adverse reactions is high in the initial ARV therapy and tends to decrease in later stages, when long-term reactions such as lipodystrophy, paresthesia and neuromotor disorders may occur [47]. In addition, factors positively associated with adverse reactions include female gender [44, 46, 48], ritonavir use compared to other PI [44, 46], progressive increase in age, hemophilia, hepatotoxicity, injecting drug use[46], and immunosuppressed patients receiving NRTI [45].

In a cross sectional study in the HIV/AIDS to describe the frequency, nature and preventability of community-acquired and hospital-acquired adverse drug reactions (ADRs) in South African hospital serving a community with a high prevalence

of (HIV) / AIDS; the contribution of ADRs to patient morbidity, hospitalization and mortality; the cardiovascular medicines and highly active antiretroviral therapy contributed the most to community-acquired ADRs at the time of hospital admission while medicines used for opportunistic infections (such as antifungals, antibiotics and antituberculosis medicines were most frequently implicated in hospital acquired adverse drug reactions and the ADRs in HIV-infected patients were found less likely to be preventable this, study was the first to be conducted in Sub-Saharan African[47].

Another cross-sectional study was carried out to document the commonly reported adverse reactions caused by ARV drugs in HIV patients in Tanzania. In this study information on drug induced adverse reactions (ADRs) in patients using HAART therapy was collected from the databases maintained in HIV clinic. A total of 7502 records of patients under ARV therapy were analyzed; the association between nevirapine (NVP) plasma concentrations and skin rashes problems was determined in 50 patients put on NVP based HAART for less than 2 weeks[48]. The study revealed that, anemia, liver toxicity, skin rash and peripheral neuropathy were the most reported ADRs. The NVP plasma level determination revealed that there was no difference between those who had experienced skin rashes and those who did not. There was a slight increase in reported ADRs between 2005 and 2006; significant number of patients changed their regimen to at least one or another HAART based treatment options. The study concluded that patients developed ARV related ADRs which are similar to those reported elsewhere in the world[48].

The findings from a three months prospective observational study of 665 adults admitted to two medical wards. Forty-one patients were admitted as a result of an ADR and 41 (6.3%) developed an ADR in hospital. Many of the ADRs (46.2%) were considered preventable, although less likely to be preventable in HIV-infected patients than in those with negative or unknown HIV status (community-acquired ADRs; *P-value 0.0001*); hospital-acquired ADRs; *P = 0.003*). Patients admitted with ADRs were older than patients not admitted with an ADR (*P-value 0.003*), but 60% of community-acquired ADRs at hospital admission were in patients more than 60 years old [46]. Among patients 60 years old and above, those HIV infected were more likely to be admitted with an ADR [odds ratio (OR) 2.32, 95% confidence interval *P-value 0.017*. Among HIV-infected patients, those receiving HAART therapy were more likely to be admitted with ADRs than those not receiving HAART (*P-value 0.0001*). No HAART-related ADRs were found to be fatal. Antibiotics and drugs used for opportunistic infections were implicated in two-thirds of hospital-acquired ADRs. The study concluded that ADRs are an important, often preventable cause of hospitalizations and inpatient morbidity in South Africa, particularly among the elderly and HIV-infected patients. Although HAART related adverse effects contributed to hospital admissions, many HIV related admissions were among patients not receiving HAART, and many ADRs were associated with medicines used for managing opportunistic infections [46, 48].

A concurrent prospective study conducted from 2001 to 2003 to assess the factors associated with adverse reactions among individuals initiating antiretroviral therapy at two public referral HIV/AIDS centers in Brazil [49]. Adverse reactions were obtained from medical charts reviewed up to 12 months after the first antiretroviral prescription. Proportional hazard model was used to perform univariate and multivariate analyses. Relative hazards were estimated with 95% confidence intervals. Among 397 charts reviewed, 377 (95.0%) had precise information on adverse reactions and initial antiretroviral treatment. Most patients received triple combination regimens including nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors. At least one adverse reaction was recorded on 34.5% (N = 130) of the medical charts; nausea (14.5%) and vomiting (13.1%) were the most common reported adverse effects. Variables independently associated with adverse reactions were: regimens with nevirapine, indinavir or indinavir/ritonavir combinations, female patients and non-adherence to antiretroviral therapy. An independent and negative association was also found for alcohol use. Adverse reactions were substantial among participants initiating antiretroviral therapy [49]. The study concluded that specially elaborated protocols in HIV/AIDS referral centers may improve the diagnosis, management and prevention of adverse reactions, thus contributing to improving adherence to antiretroviral therapy among HIV-infected patients.

In one of the most recent prospective cohort study that was performed to assess the HAART induced adverse drug reactions in Iranian Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome Research Center during years 2005-2007. Adult patients who infected with HIV and newly started on ART were included in this study and followed laboratory and clinically for the development of any ADRs for at least 6 months. During this study 87.6% of patients showed at least one ADR. Prevalence of ADRs based on affected organ was: gastrointestinal (GI) (63.7%), hematological (32.6%), neurological (30%), cutaneous (22%), musculoskeletal (21.3%), hepatic (20%), metabolic (18.6%), and renal (2.6%) adverse effects.

The most important results of this study were finding of hematological ADRs as the most common cause of ART interruption, supporting the hypersensitivity nature of antiretroviral induced hepatotoxicity especially cholestasis and new finding of the significant positive correlation between hepatitis C virus co-infection and the occurrence of ART induced skin reactions [50].

In retrospective study on 95 horizontally HIV-infected patients to evaluate the incidence and spectrum of medium and long term adverse reactions associated with HAART regimens in multi experienced HIV/AIDS patients aged 0-14 years, treated in Craiova Regional Center of Survey and Monitoring of HIV/AIDS – Romania, between 1996 and 2003 with more than three HAART regimens. Adverse reactions were present in 36 patients (37.89%). Minor and mild gastro-intestinal reactions (not imposing ARVT suspending) were found in 12 cases (12.63%). Hepatotoxicity, revealed by high cytolisys levels, was registered in 8 cases (8.42%) and disturbance of bilio-excretory

function in 6 patients (6.31%), in 3 cases (3.15%) the change of therapeutic scheme being imposed. Nephrolithiasis was present in 6 patients (8.45%) out of 71 treated with IDV (after an average treatment period of 6 months), 4 cases (5.63%) needing therapeutic replacement. Out of 78 patients treated over 1 year with PI, 3 (3.84%) presented dilatative cardiomyopathy and 11 (14.1%) pulmonary hypertension. Peripheral neuropathy post NRTI treatment was seen in 8 cases (8.42%). Among cutaneous manifestations, hypersensitivity to Abacavir imposed ceasing its administration in 2 cases; cutaneous rush after NNRTI administration was found in 15 patients (15.78%); xerosis in 21 cases (22.1%), mainly associated with IDV treatment. Lipid metabolism disturbances were met in 28 patients (29.47%) treated with IP for more than 6 months. Severe hematological changes were found in 6 cases (6.31%). The study concluded that HAART adverse reactions represent an important difficulty in HIV medicine, an attentive evaluation of treatment onset and HAART regimen being necessary [51].

Materials And Method

Study design

This study combines both quantitative and qualitative approaches. HIV/AIDS specific Adverse Drug Reactions (ADRs) case report form (See appendix 1) containing all the basic information for reporting of adverse drug reactions as per WHO guidelines was designed based on a consultation from an expertise in patient safety from the WHO essential medicines and pharmaceutical policy department of HIV/AIDS and through this department the form was also validated.

The reporting form was designed in such a way to be capable of providing quantitative analysis and statistical comparisons using non parametric methods, the form also contain space for comments which will allow the health care professionals to express their own individual views which may help in the analysis and causality assessments of the adverse effects that will be carried out by the pharmacovigilance team of the Sudan pharmacovigilance center.

The Adverse Drug Reactions Case Report Form is divided in to four main parts and it seeks data regarding patient demographic information, laboratory tests and results, suspected adverse drug reaction, suspected drug(s) or medication and reporter information.

List of some relatively known; frequent and infrequent adverse reactions associated with HAART and other drugs used in the treatment of opportunistic infections associated with HIV/AIDS was provided at the back of the reporting form to guide the reporters.

These adverse effects are referenced from SNAP [18] and other Medicines Handbook and labeled according to the WHO adverse drug reactions terminology (WHO – ART) December 2008[15]. The list is not completely comprehensive as not all recognized adverse effects have been given. In addition, there are some rare adverse effects which have not been listed as well. So the reporters were advised to report all suspected adverse drug reactions.

The main variables in the form are:

- Age, Weight and Sex
- Description of adverse reaction(s)
- Duration of the reaction(s)
- Seriousness of the reaction(s)
- Adverse reaction(s) outcome
- Suspected drug(s) that cause the reaction(s)

These variables was measured and analyzed based on a designed scale on SPSS.

Population and samples

Participants were HIV-infected adult patients eighteen years old and above; recruited at HIV/AIDS public referral center (Voluntary Testing and Counseling Center) at Basha`ar Hospital, Khartoum, Sudan, from May to September 2009. Public rather private, availability of HAART medications, and good communication with the pharmacovigilance department are the strong reasons that satisfied the criteria of selecting the VCT center at Basha`ar Hospital.

Patients come to this VCT center either for HIV testing and diagnosis and subsequently counseling to take their first HAART therapy; or for routine referral and follow-up to obtain their next month medications. The patients were recruited for an ongoing prospective HARRT associated adverse effects study. Information on clinical adverse reactions and on reactions related to health care utilization variables was collected from individuals who complain of any clinical symptoms.

The total numbers of patients registered in this hospital (VCT – Center) are 255 individual, among them only 166 are referred to take their HAART regimens in regular bases during the study period; those patients were considered the population of this study and they were followed for the period of study.

Outcome and exposure variables

An adverse reaction to HART was defined as any undesirable effect or symptom registered in the HAART specific ADRs case report form by the physician responsible for the routine treatment of the patients, at the VCT, following the routine examination of HIV/AIDS patients. We considered only those reactions which were specifically reported as resulting from at least one HAART regimen according to the physician's judgment. The adverse reaction reported in the ADRs case report form was considered the outcome for analysis. A standardized list was used to code the adverse reactions [15, 52]; gastrointestinal (nausea, vomiting diarrhea), dermatological (epidermal necrolysis, skin reactions, rashes, allergy), and neurological or CNS effects (insomnia, nightmares, dizziness, depression) and other adverse reactions.

The seriousness, severity of adverse reactions and reaction outcomes were assessed on the basis of whether intervention was required to prevent persistent incapacity or disability, the reaction caused or prolonged hospitalization and caused death or recovered.

Methods of data analysis

Statistical analysis

Data was analyzed by using the Statistical Package for the Social Sciences (SPSS) to relate variables and/or compare groups in terms of variables; so that inferences can be drawn from the sample to population.

Descriptive analysis was performed to characterize the number and type of adverse reactions. The magnitude of the association between putative factors and ADRs was estimated by the relative hazard, with a 95% confidence interval, using statistical chi square test

Causality assessment

Causality assessment was performed according to the WHO guidelines, the WHO – UMC system for causality assessment was used to correlate the drug to the suspected adverse effects (30, 15). This system is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation.

Ethical considerations

Ethical issues that could arise during data collection, analysis and writing are confidentiality, anonymity and biased writing. These issues were addressed as follows:

• Letters identify the purpose, impact and outcome of the study was sent to the manager of the VCT center at Bashaer hospital and formal permission to conduct this topic was obtained (Appendix 2).

• Covering letter explaining the aim of the study and its expected outcome and acknowledging that the reporters and patients' confidentiality will be protected during data collection and analysis was provided for all the health care professionals participated in this study (Appendix 3).

• Adverse reaction case report form contains no names and the patient's identity is held in strict confidence and protected to the fullest extent. Neither the researcher nor the pharmacovigilance staff are expected to and will not disclose the reporter's identity in response to a request from the public.

• Words used in writing were not falsified or invent findings to meet the writer needs or any other special needs.

• All the information will remain confidential and may use for an academic purpose only.

The project proposal was approved by the Ethics Research Committee of the University of Medical Sciences and Technology.

Justification of methodology

Literature review describes the previous knowledge and ideas on this topic, strength and weaknesses. It provides a framework for establishing the importance of the study as well as a benchmark for comparing the results with other findings. It relates a study to the larger, ongoing dialogue in the literature, filling in gaps and extending prior studies [24].

The advantages with the adverse reaction case report form are that it is simple and cheap and comply with the procedure of spontaneous reporting [15, 28]. It is the most convenient methods in case of this dissertation and at the same time it can generate more data from the users of HAART, which could then be generalized.

Standardized measurement that is consistent across all case report form ensures that comparable information is obtained about every ADRs report form [14].

The concurrent use of close-ended questions with a chance for comments in a survey will enable the collection of quantitative and qualitative data simultaneously during a single data collection phase. Data, then, could be resided side by side as two different pictures that provide an overall composite assessment of the problem [14, 29].

Results

Among the 257 patients recruited, 166 (64.5%) received their HAART regimens regularly. At least one adverse reaction was reported by health care professional as a result of one of the three HAART regimens used during the period of the study, leading to an incidence rate of (0.44)

Overall, 226 adverse reactions were registered, with epidermal necrolysis and other form of dermatological adverse effects (15.5%), gastrointestinal adverse effects (15%) and peripheral neuropathy (14.2%) being the most common reported ADRs (Table 1 -4).

Table 1: Association between HAART Treatment Regimens and Adverse Drug Reactions among the studied patients using Cross-Tabulation Statistical Chi-Square Test (n=74)

HAART Regimen	Anemia		Peripheral Neuropathy		Redness of the Eye and Optical Neuritis ADRs		Neurological ADRs		Respiratory ADRs	
	Present (%)	Absent (%)	Present (%)	Absent (%)	Present (%)	Absent (%)	Present (%)	Absent (%)	Present (%)	Absent (%)
Regimen (1a)	4.7	95.6	65.1	34.9	9.3	90.7	14	86	32.6	67.4
Regimen (1b)	8.3	91.7	16.7	83.3	70.8	29.2	58.3	41.7	8.3	91.7
Regimen (1c)	66.7	33.3	0	100	0	100	0	100	16.7	83.3
P - value	*.000**		*.000 **		*.000**		*.000**		*.047**	

*P – value less than 0.05 are considered statistically significant

Alongside with HIV/AIDS, Tuberculosis (TB) was also present as co-infection in (33.8 %) of the studied patients group.

Optical neuritis and other form of ophthalmic adverse reactions have being reported the most occurring ADRs (Table2).

Table 2: Association between presences of TB – Co infection and Adverse Drug Reactions among the studied patients using Cross-Tabulation Statistical Chi- Square Test (n=74)

Presence of TB	Necrolysis and other Dermatological ADRs		Peripheral Neuropathy		Redness of the Eye and Optical Neuritis ADRs		Neurological ADRs		Respiratory ADRs	
	Present (%)	Absent (%)	Present (%)	Absent (%)	Present (%)	Absent (%)	Present (%)	Absent (%)	Present (%)	Absent (%)
Present	32.0	68.0	24.0	76.0	64.0	36.0	48.0	52.0	28.0	72.0
Absence	57.1	42.9	53.1	46.9	10.2	89.8	16.3	83.7	22.4	77.6
P - value	*.035 **		*.015 **		*.000**		*.005**		*.04**	

*P – value less than 0.05 are considered statistically significant

There were 24 patients that recorded hospitalized and one record of death due to the adverse reactions; which could not be confirmed or rolled out.

However, the incidence of adverse reactions was higher within the female population (64.9 %). And the reactions outcome varies from life threatening to a few death cases that occurs only within the male population (Table 3).

Table 3: Percentage of Adverse Reactions Outcome within the Patients Gender among the Studied Patients

Patients Gender	Reactions Outcome				
	Life Threatening (%)	Caused or Prolonged Hospitalization (%)	Persistent Incapacity or Disability (%)	Death (%)	Recovered (%)
% within The Male Patients	3.8	30.8	7.7	3.8	53.8
% within The Female Patients	8.3	35.4	2.1	0	54.2
Total % within The Patients Gender	6.8	33.8	4.1	1.4	54.1

The result have shown that utilization of multidrug regimens for treatment of TB along with the HAART regimen has led to undesirable reactions outcomes of varying degrees (Table 4)

Table 4: Percentage of Adverse Reactions Outcomes within the TB Co - infection among the Studied Patients

TB Status	Reactions Outcome				
	Life Threatening (%)	Caused or Prolonged Hospitalization (%)	Persistent Incapacity or Disability (%)	Death (%)	Recovered (%)
% within The Presence of TB	4	44	0	0	52
% within The Absence of TB	8.2	28.6	6.1	2	55.1
% within The Total Patients	6.8	33.8	4.1	1.4	54.1

Discussion

The study found a high cumulative incidence of adverse reactions due to HAART (44.5%), similar to those observed by other investigators [36]. Most of the adverse reactions occurred during the first six month of treatment, explaining the observed pattern of adverse reactions compatible with the incidence of acute, common and nonspecific events. In agreement with previous studies, gastrointestinal complaints and epidermal necrolysis and other dermatological adverse effects were the reactions most frequently reported [36, 37, 53]. However unlike previous studies; peripheral neuropathy was counts for (65.2%) of the adverse reactions within regimen (1a). In addition, despite limited information, most reactions were light to moderate.

Although the list of frequent and infrequent adverse effects was provided at the back of the reporting form; very small numbers of generic events (e.g., Side effects, Intolerance) were recorded by health care professionals as a result of HAART use, but precise information on the type and frequency of such events could not be obtained. This suggests that definitions of reactions and their diagnosis have not been completely standardized in routine clinical practice in Sudan; nevertheless they were frequently occurring at the beginning of therapy.

As demonstrated by Pfaffenbach et al. [59], adverse reactions are not always identified with the proper code according to the International Classification of Diseases and/or the World Health Organization Adverse Reactions Terminology (WHO - ART). It is possible that not all patients' complaints are reported as adverse reactions, thus generating an underestimation of their true incidence in the studied population.

Change of regimens (HAART switch), symptomatic and/or supportive treatment with antihistamines and pyridoxine were identified as interventions used for the management of adverse reactions to HAART in the studied population. Dose adjustment was not performed in any patient experiencing adverse reactions, this indicating that change of regimens and symptomatic treatment of the events were the preferred option adopted by physicians in order to minimize and prevent new events.

Similarly, and in agreement with other investigators [38, 41] the incidence of adverse reactions was higher among the females (64.9 %). The increased risk of adverse reactions among women could be explained by differences in the absorption and metabolism rates of these drugs, with the involvement of gender-specific cytochrome P450 isoenzymes. Moreover, other biological differences such as blood flow, body mass, and hormonal changes during the menstrual cycle can explain this finding [44, 54].

Descriptive analysis indicate that Tuberculosis and AIDS Co-infection is present in 25 (33.8%) of the studied patients. Using Cross-Tabulation Statistical Chi-Square Test; the study found a very strong association between presence of TB - AIDS Co-infections and some specific adverse reactions among the studied patients. This very high incidence of adverse reactions in TB – HIV/AIDS co – infections may be due to the reasons that both drug classes may share the same pass way for adverse reactions [41].

However, formal studies evaluating the influence of Tuberculosis on the intensity or type of adverse reactions due to HAART uses are lacking, with the consensus being that caution should be used, especially when prescribing HARRT to patients with TB [60]. Thus, the positive association between TB and adverse reactions observed in the present analysis should be interpreted with caution considering that many risk factors associated with Tuberculosis may affect the occurrence of adverse reactions which can't be rolled out this may include; the nutritional status of the TB infected patients and the drugs used in the treatment of TB, this are all factors that may have not be well reflected in this study.

The incidence of at least one adverse reaction was higher among patients given HAART regimens contain at least one of these drugs; Stavudine (D4t), Lamivudine (3TC), Nevirapine (NVP) and Efavirenz (EFV) in a combination as regimen (1a) or (1b). Previous studies have shown the increased risk of adverse reactions associated with regimens including RTV combinations [36, 37]. Similarly, the use of EFZ among patients initiating HAART therapy with NNRTI has been recommended to be the first choice due to its lower toxicity compared to NVP [61].

Data solely based on spontaneous reporting are also known to lack adequate reliability. As shown by others, medical professionals can inappropriately record symptoms or adverse effects described by patients [37, 41, 63], a fact that may have resulted in an underestimate of this event in our study analysis. In addition, categorization of most variables into two levels due to a relatively small size of our sample may have impaired complete adjustment, in theory, this could overestimate the incidence of adverse reactions and should therefore be interpreted with caution since it may potentially leave some residual confounding that should be further explored in future analyses.

In addition, the patient's description of reaction severity can be inconsistent with the clinical interpretation (ie, some patients may overemphasize symptoms, whereas others underemphasize symptoms), and this must be considered when determining the management of adverse reactions.

On the other hand, medical procedures such as dose adjustment or HAART switch, common causes of adverse reactions, must be notified by health care professionals, as part of the Sudan HIV/AIDS policy, possibly generating data on more severe reactions.

Among the 257 patients recruited, Regimen (1a) of the HARRT has shown to be the mostly used regimen among the patient population (Figure 1).

Regardless of which HAART regimen caused the adverse drug reactions it appears that most of the reactions out comes have being recovered (Figure 2).

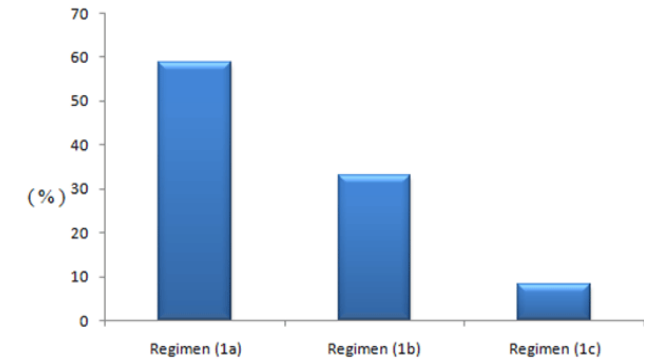

Figure 1: Distribution of HAART Regimens among Studied Patients

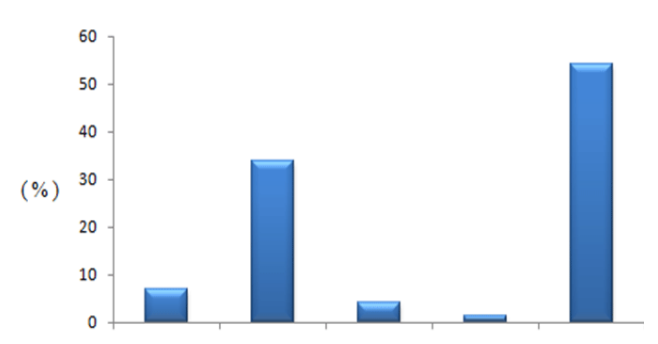

Figure 2: Reactions outcomes Among Studied Patients

Recommendations

In the HIV positive patients with advanced infection, efficacy between the three regimens of HAART is similar, but there is a tendency to require more withdrawal due to sever adverse reactions. Although these reactions are common and often predictable, their management must be individualized. Several factors will affect the management of adverse reactions, including co morbid conditions; the patient's other current medications, the availability of alternative regimens, and the patient's history of medication intolerance.

Therefore; providing a list of terms used in reporting of adverse reactions adapted to the drugs used in the management of HIV/AIDS in accordance to the International Classification of Diseases and/or WHO – ART well stimulate the health care professionals in generating more reliable reports with high quality.

Finally, I should emphasize the importance of the establishment of standardized protocols for reporting adverse reactions at public referral HIV/AIDS centers and VCTs. The standardization of adverse reactions due to HAART use may help health care professionals to improve the recognition, management and prevention of this event. Treatment of the adverse reactions, including dose adjustment and the choice of an appropriate regimen, is a key strategy for improving adherence among patients initiating therapy with HAART and subsequently reduces the patient suffering and improves the quality of life.

Conclusion

The study was clearly illustrates the prevalence and extent of adverse reactions that most commonly associated with HAART uses in Sudanese HIV/AIDS infected persons.

Despite the limitations and observations of this study, and considering this to be the first study on adverse reaction among patients initiating HAART in Sudan, we believe our findings from this study are suitable and valid for comparison purposes within our Sudan national AIDS program.

The study also addresses the challenges faced by resource-poor settings and the methods to overcome these challenges by establishing simple and cheap system for the reporting of adverse reactions in HIV/AIDS referral clinics; which can be further adopted to other public health program.

The ADR reports after analysis will remain at the Sudan Pharmacovigilance Program and will be used to maintain the Sudan membership at the WHO international drug monitoring program.

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