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Review Article

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Adverse drug reactions in HIV/AIDS patients on highly active antiretro viral therapy: a review of prevalence

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Abstract

Antiretroviral therapy (ART) is associated with a variety of side effects, ranging from mild intolerance to life-threatening side effects. Short-term adverse reactions include nausea, vomiting, diarrhea, rash, hypersensitivity reactions, urticarial reactions, erythema multiforme, toxic epidermal necrolysis or Stevens-Johnson syndrome, infection liver toxicity, drowsiness and vivid dreams. Long-term side effects include lipodystrophy, lipoatrophy, dyslipidemia, diabetes, and skin, nail, and hair abnormalities. When starting ART, HIV-infected patients may frequently experience a variety of side effects such as rash, hair loss, hypersensitivity syndrome reactions, urticaria or erythema multiforme, Stevens-Johnson syndrome, known as manifested by a short-term course of side effects. A large number of patients have abnormal blood sugar and lipid profiles when using all groups of ARV drugs despite their relatively young age; Hyperlipidemia has been associated with HIV PI use and is more common and more severe than hyperlipidemia in HAART-naïve patients. Dyslipidemia, hyperglycemia, and lipodystrophy are cardiovascular risk factors in these patients. Hypertension is associated with established risk factors and is common in HIV-infected individuals. However, long-term use of HAART/ARV is necessary to control HIV infection.

Keywords: *prevalence, adverse drug reaction, HIV, AIDS, HAART*

Introduction

WHO, defines an adverse drug reaction (ADR) as a response to a drug that is noxious and unintended and that occurs at doses used in humans for prophylaxis, diagnosis, therapy of disease or for the modification of physiologic function. This excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors plus the prevalence of ADR defined as the proportion of the study population with ADR [1-3].

Antiretroviral therapy (ART) is associated with a wide range of ADRs, varying from mild intolerance to life-threatening side effects. The short-term adverse effects include nausea, vomiting, diarrhea, rash, hypersensitivity reactions, urticarial reaction, erythema multiform, toxic epidermal necrolysis or Stevens-Johnson syndrome, hepatotoxicity, drowsiness and vivid dreams [4-5]. Intermediate adverse effects are anemia, neutropenia, bone marrow suppression, hyperpigmentation of skin, nails and mucous membranes, lactic acidosis, peripheral neuropathy, and pancreatitis [6]. Long term adverse effects include lipodystrophy, lipoatrophy, dyslipidemia, diabetes, abnormalities in the skin, nail, and hair [7].

Globally as of 2018, around 37.9 million people worldwide are suffering from Human Immunodeficiency Virus (HIV). 1.7 million people became newly infected with HIV, 770,000 people died from AIDS related illnesses, 74.9 million people have become infected with HIV since the start of the epidemics. Still, about 32.0 million people have died from AIDS-related illnesses since the start of the epidemic [8]. Additionally, as of end 2018 the total

number of people living with HIV showed that 36.2 million were adults (> 15 years), 1.7 million were children below the age of 15 years and an estimated 8.1 million people did not know that they were living with HIV. Furthermore, as of the end of June 2019, 24.5 million were accessing antiretroviral therapy (ART).In 2018, 23.3 million people living with HIV were accessing ART, up from 7.7 million in 2010. The percentage number of people living with HIV accessing treatment being 62%, and also adults aged 15 years and older accessing treatment being 62% as did 54% of children below 15 years. 68% of female adults aged 15 years and older had access to treatment. However, just 55% of male adults aged 15 years and older had access. 82% of pregnant women living with HIV had access to antiretroviral medicines to prevent transmission of HIV to their child in 2018. New HIV infections have been reduced by about 40% since the peak in 1997. In 2018, around 1.7 million were newly infected with HIV, compared to 2.9 million in 1997. Since 2010, new HIV infections have declined by an estimated 16% from 2.1 million to 1.7. Also, according to the **90-90-90** strategy, in 2018 79% of people living with HIV knew their status and among them, 78% were accessing treatment and among those accessing treatment, 86% were virally suppressed [9-10].

In women, around 6000 young women aged 15-24 years become infected with HIV every week. In sub–Saharan Africa, four in five new infections among adolescents aged 15-19 years are in girls. Young women aged 15-24 years are twice as likely to be living with HIV as men. More than one third (35%) of women around the world have experienced physical and or sexual violence at some time in their lives. In some regions, women who have experienced physical or sexual intimate partner violence are 1.5 times more likely to acquire HIV than women who have not experienced such violence. Key populations and their sexual partners account for about 54% of new HIV infections globally, 64% of new infection in western and central Africa, 25% of new infections in eastern and southern Africa. The risk of acquiring HIV is 22 times higher among men who have sex with men, 22 times higher among people who inject drugs, 21 times higher for sex workers and 12 times higher for transgender people [11-12].

The common ADRs in HIV patients on HAART

ADRs are harmful and unintended reactions or adverse or noxious reaction to medications given at standard doses. Although the introduction of HAART has led to a significant reduction in AIDS related morbidity and mortality, the increasing adverse drug reactions (ADR) related to HAART had its utility and compliance weighed against beneficial effects. ADRs play a major role in determining adherence to HAART and adherence is perhaps the most significant determinant of a regimen's success [13].The spectrum of adverse events is wide and varied, being difficult to identify the principal cause. At the beginning of the ARV treatment, HIV infected patients can frequently exhibit a wide variety of ADRs such rashes, hair loss, hypersensitivity syndrome reactions, urticarial, or erythema multiform, stevens-Johnsonsyndrome, which present as short-term course of adverse reactions occurring within the first few Weeks of ART initiation.

A large number of patients exhibited abnormal glycemic and lipid profiles with all classes of ARV agents despite the relatively young age; the hyperlipidemia has been associated with the use of HIV PIs which is more common and more severe than hyperlipidemia observed in HAART naïve. Hyperlipidemia and hyperglycemia (reflecting insulin resistance) and lipodystrophy are increasingly described ADRs of PIs. Still the NRTIs, especially stavudine-d4T has been associated with lipodystrophy [14]. Lipodystrophy is characterized by changes in body fat distribution including increased waist circumference, increased breast size, and fat accumulation in the neck, cheeks, and buttocks. Dyslipidemia, hyperglycemia and lipodystrophy are cardiovascular risk factors in these patients. Hypertension is associated with established risk factors and is common among HIV-infected individuals [15]. Also, studies show that HIV infected females were significantly more likely to experience an ADR than males. Nevertheless, prolonged use of HAART/ARVs is necessary for control of HIV infection [16].

Non-nucleoside reverse inhibitor (NNRTI) and NtRTIs are known for their mitochondrial toxicity which mediates several forms of ADRs which include the following; myopathy, peripheral neuropathy, hepatic steatosis, lactic acidemia, peripheral lipoatrophy and pancreatitis among others. These drugs are furthermore implicated in the occurrence of hypersensitivity characterized by erythematous, maculopapular, pruritic and confluent rash and are also involved in lipodystrophy which However is more predominantly associated with protease inhibitor (PI) [15].

Prevalence of ADRs in HIV patients on HAART

ADRs are a noxious and unintended response or an adverse or noxious reaction to a medicine that occurs at normal therapeutic doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function [17]. ADRs and events are a serious problem increasing morbidity and mortality and health care costs, incidence literally suggests the measure of risk that a person or the proportion of the study population on HAART will develop ADRs.

ADRs is with most prolonged drug therapies, the risk to development of ADRs usually shoots and therefore predictable. Of the prevalent ADRs in patients on HAART, over 90% are predictable, these include hepatitis, which is most notable with regimens including non-nukes, the unpredictable ADRs being less than 5% and include pancreatitis, depression and Steven-Johnson's syndrome, still, among the prevalent ADRs, a section of them are preventable while the others aren't preventable [18]. The unpreventable include rash, urticarial of skin and appendages, while one of the most common ADRs, anaemia usually results from the first few months of initiation of the therapy containing Zidovudine, a myelo-suppressive drug, can be avoided by preventing its use in patients with a hemoglobin level of less than 8g/dl. In terms of severity, up to 34.8% are mild, 58.8% are moderate while the remaining 6.4% are severe and include lactic acidosis, lipodystrophy and nail discoloration. Among patients affected by hyperlipidemia, 47.3% are affected by hypertriglyceridemia while 36.1% and 22.6% are affected by hypercholesterolemia and hyperglycemia respectively [15].

With incidence of ADRs reported by various surveys to be anywhere as low as 19.5% and as high as 86%, the patterns of occurrence of these are more clearly defined along the lines of sex, age, co-morbidities and Co-Infections, duration of the therapy and the presence or absence of concomitant therapy [19]. Most notable sex differences have been observed with NRTIs, PIs, and NNRTIs. Women have been observed to suffer more from the mitochondrial toxicity mediated ADR lactic acidosis, a severe rare but fatal ADR associated with regimens containing NRTIs, compared to men who have displayed tolerance to such regimens. Among the non-nucleoside reverse inhibitor (NNRTI), nevirapine, characteristically used for PMTCT during pregnancy is common part of HAART that usually causes a rash as its ADR as Ill as hepatitis, the nevirapine-associated rash is more prevalent in women than in men, and a similar trend is noted with the PIs as regards gastric intolerance [15]. These sex differences are postulated to be brought about by the difference in BMI, fat composition and hormonal effects on drug metabolism among others [20].

Conclusion

The prevalence of ADRs is common among females which suggests more gender-based programs on awareness and how to mitigate ADRs are needed, HIV patients with co-morbidities should be observed routinely as their co-medication is highly linked to ADR development. Also, ADRs are very common to patients initiating HAART therapy which requires the newly initiated patients to adhere to the therapy irrespective of the ADRs as they decrease with time.

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