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Original Research Article

Monitoring adverse drug reactions in patients on TDF+3TC+EFV in a tertiary care hospital in Eastern India: a prospective observational study

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ABSTRACT

Background: Recently, the National Aids Control Organisation (NACO) in India advocated and recommended the use of tenofovir, lamivudine and efavirenz as a fixed-dose combination in initiating ART in all future treatment-naïve patients. The present study was thus undertaken to assess the nature and extent of safety concerns with this regime.
Methods: A prospective observational study was carried out in the outpatient setting of nodal ART centre of Eastern India. A total of 242 patients on various ART regimens were studied for suspected ADRs over one year. Adverse event history, medication history and other relevant details were captured. Causality and severity of each reported ADR were duly assessed.
Results: Out of 242 PLHIV put on this regimen, 75 patients did not encounter any adverse reactions during the entire study period. Out of remaining 167 patients who presented with a total of 451 ADRs, maximum ADRs were attributed to various psychiatric disorders which included insomnia, dizziness, drowsiness etc, which were followed by gastrointestinal disorders including anorexia, flatulence, nausea, vomiting etc. Dermatological complications included rashes, itching, SJS, pigmentation of nails, skin hyper pigmentation respectively.
Conclusions: The study enables to obtain information on the pattern of adverse drug reactions associated with treatment naïve PLHIV put on first line antiretroviral regimen comprising of once daily dosing of tenofovir, lamivudine, efavirenz. Need of intensive monitoring for ADRs in ARTs followed with proper patient counselling regarding its nature can lead to better compliance to the therapy.

Keywords: Adverse drug reactions, Efavirenz, HIV, Lamivudine, Tenofovir

INTRODUCTION

Since scientists identified the human immunodeficiency virus (HIV) as the cause of acquired immunodeficiency syndrome (AIDS) in 1983, it has spread relentlessly, causing one of the most devastating pandemics ever recorded in human history.[1] Since the beginning of the epidemic, more than 70 million people have been infected with the HIV virus and about 35 million people have died of HIV. Globally, 36.7 million (34.0-39.8 million) people were living with HIV at the end of 2015. An estimated 0.8% (0.7-0.9%) of adults aged 15-49 years worldwide is living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Sub-Saharan Africa remains most severely

affected, with nearly 1 in every 25 adults (4.4%) living with HIV and accounting for nearly 70% of the people living with HIV worldwide.[2]

The advent of highly active anti-retroviral therapy (HAART) in 1997 changed the natural progression of the disease caused by HIV, thus reducing viral replication, increasing the number of CD4 lymphocytes and improving their function, re-establishing the defenses of the host and improving chances of survival.[3] A reduction in the rate of opportunistic infections and hospitalizations in adults infected with AIDS after 6-12 months of HAART intervention is well documented.[4] Decreases in hospitalizations and deaths result in a substantial reduction in health care costs associated with infected patients.[5]

Medications enhance both quality of life and longevity. Antiretroviral drugs are medications used for the treatment of infection by retroviruses, primarily HIV. The goals of antiretroviral therapy (ART) in HIV infections comprises of prolongation of life and improvement in quality of life with greatest possible reduction in viral load for as long as possible. However, attempts to achieve these goals with standard antiretroviral pharmacotherapy are fraught with a diverse range of unwelcome adverse drug reactions (ADRs). As per WHO guidelines, the first-line ART should consist of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI). Recently, the National Aids Control Organisation (NACO) in India advocated and recommended the use of tenofovir (TDF), lamivudine (3TC) and efavirenz (EFV) as a fixed-dose combination in initiating ART in all future treatment-naïve patients. In the event of drug toxicity and severe adverse drug reactions, the offending drug(s) must be discontinued and changed to other drugs from within respective ARV options.

Studies comparing different standard regimens showed moderate-quality evidence indicating that a once-daily combination of tenofovir, lamivudine and efavirenz is less frequently associated with severe adverse events and has a better virological and treatment response compared with other once- or twice-daily regimens.[6,7] However, they are not devoid of adverse reactions. ADR surveillance is an integral component of monitoring and evaluation in ART program. The goal of monitoring is to detect the early toxicities and adverse effects in order to support the safe use of ART, thus improving the quality of care and treatment outcomes and to inform national guidelines and global policies on the use of first line ART in adults. Tenofovir induced nephrotoxicity, lamivudine induced skin rash, and efavirenz induced hepatotoxicity are important concerns. However, attributing a single drug to a particular adverse event is cumbersome, as HAART comes as a three drug regimen. There is dearth of studies assessing the safety, tolerability and long term effects of this regimen. The present prospective study thus assesses the nature and extent of safety concerns with this regime.

METHODS

Study design, duration and setting

A prospective observational clinical study was carried out for a period of one year among PLHIV receiving ART in the outpatient setting of a nodal ART centre of eastern India.

Inclusion criteria

All treatment naïve subjects of either sex aged 18 years or above on ART were included in the study.

Exclusion criteria

Following were excluded from the study:

- Subjects having treatment modifications due to virological or immunologic failure
- Pregnant women
- Lactating mothers
- Patients having any other co morbidities like psychiatric illness, diabetic mellitus, hypertension, chronic kidney disease, etc.

Data collection and analysis

Institutional ethics committee approval was taken prior to the initiation of the study and written informed consent was obtained from all subjects before their inclusion in the study. Data regarding patient demographics and clinical information were collected in a pre-structured proforma. ADR diagnosis was based on patient complaints and/or morphological changes noticed by physicians during routine clinical exam. Adverse event history, medication history and other relevant details were captured in a format as adopted in the Pharmacovigilance Programme of India (PvPI). Causality of ADR was assessed by Naranjo's ADR probability scale and WHO-UMC causality assessment scale respectively.[8,9] The severity of each reported ADR was assessed using Hartwig and Siegel Scale.[10] Descriptive statistical analysis of the obtained data was performed.

RESULTS

Baseline demographics

The present study included a total of 242 PLHIV who were put on first line ART regimen containing tenofovir, lamivudine and efavirenz. Out of these 242 PLHIV, 53.72% of the study population were males (n=130). Patients belonging to 31 to 40 years of age group represented the maximum study population (49.17%), followed by those belonging to 41-50 years (39.2%). Age group analysis has been duly represented in Table 1. Other baseline demographics have been represented in Table 2.

Table 1: Age group analysis.

AGE group (in years)	Frequency (%)
18-20	0 (0)
21-30	21 (8.6)
31-40	119 (49.17)
41-50	95 (39.3)
51-60	7 (2.9)
>60	0 (0)

Table 2: Baseline demographics.

	Frequency (%)
Sex Ratio	
Male	130 (53.71)
Female	112 (46.3)
Religion	
Hindu	166 (68.6)
Muslim	76 (31.4)
Others	0 (0)
Mean Height (in cms)	164.23±5.131
Mean Weight (in kg)	57.04±8.250
Marital Status	
Unmarried	54 (22.3)
Married	167 (69.0)
Separated	5 (2.1)
Others	16 (6.6)

Out of 242 PLHIV put on TDF+3TC+EFV regimen, 167 patients reported with a total of 451 adverse drug reactions. Out of 167 patients reporting with one or more ADRs, 49.7% belonged to 31-40 years age group followed by 40.12% belonging to 41-50 years group (Table 3).

Table 3: Age group analysis of patients reporting with one or more ADRs.

AGE group (in years)	Total patients screened [n (%)]	Patients encountering one or more ADRs [n (%)]
18-30	21 (8.6)	13 (7.78)
31-40	119 (79.8)	83 (49.70)
41-50	95 (39.2)	67 (40.12)
51-60	7 (2.9)	4 (2.39)
>60	0 (0)	0 (0)

Out of 242 patients, 75 patients did not encounter any adverse reactions during the entire study period. Out of remaining 167 patients, 83 patients encountered with one ADR, 57 patients with two ADRs and 27 patients with three or more ADRs. (Figure 1)

As per various organ system classifications, each adverse drug reaction was distributed to obtain an ADR Spectrum as represented in Figure 2. Analysis revealed that 43.24% ADRs were attributed to psychiatric disorders, followed by 21.95% and 10.2% attributing to gastrointestinal and musculoskeletal disorders respectively.

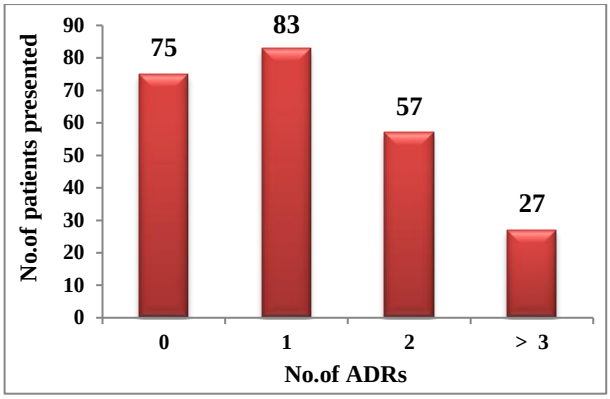

Figure 1: Distribution of ADRs

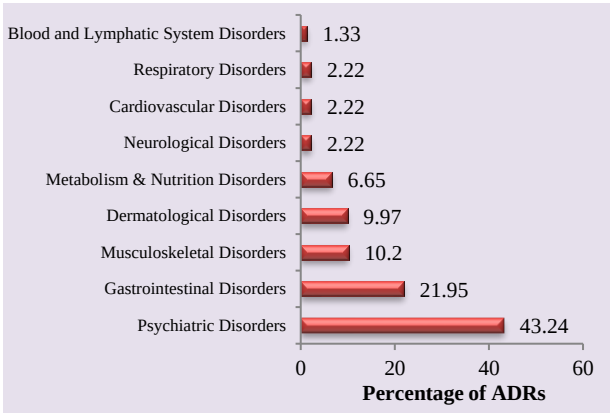

Figure 2: Distribution of adverse drug reactions as per organ system classification.

Adverse drug reaction profile

A total of 451 ADRs were reported from 242 study subjects. Table 4 represents the entire ADR profile which was monitored in a total time period of one year.

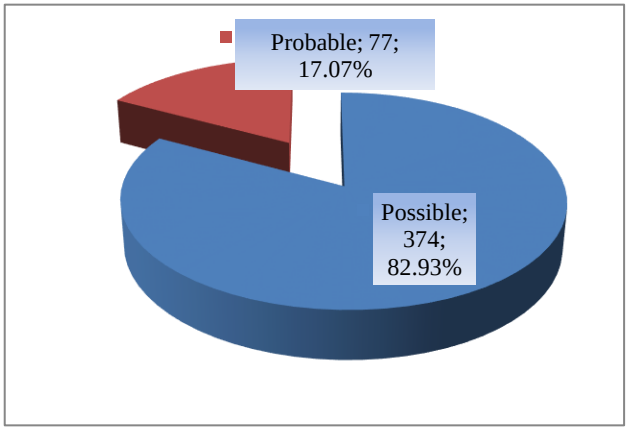

Figure 3: Causality assessment of the reported ADRs using Naranjo's algorithm.

Causality assessment of the total reported adverse drug reactions were performed using both Naranjo's algorithm and WHO-UMC causality assessment scale.

Table 4: ADR profile of 242 study participants.

ADR description	Frequency (n)	% of total ADRs
Psychiatric disorders		
Insomnia	35	7.76
Dizziness	58	12.86
Drowsiness	41	9.09
Headache	50	11.09
Numbness	1	0.22
Impaired concentration	6	1.33
Mood swings	4	0.88
	195	43.24
Gastrointestinal disorders		
Anorexia	8	1.77
Flatulence	7	1.55
Nausea	27	5.99
Vomiting	19	4.21
Abdominal pain /cramps	11	2.44
Diarrhoea	19	4.21
Dyspepsia	8	1.77
	99	21.95
Musculoskeletal disorders		
Generalized Weakness	33	7.32
Body ache	8	1.77
Muscle cramps/pain	5	1.11
	46	10.20
Dermatological disorders		
Rashes	29	6.43
Itching	7	1.55
Stevens Johnson Syndrome (SJS)	2	0.44
Pigmentation of nails	5	1.11
Skin hyper pigmentation	2	0.44
	45	9.97
Metabolism and nutrition disorders		
Increased liver enzymes	22	4.87
Increased lipid levels	8	1.77
	30	6.65
Neurological disorders		
Peripheral neuropathy	8	1.77
Tremors	2	0.44
	10	2.22
Cardiovascular disorders		
Palpitation	5	1.11
Moderate increase in BP	4	0.88
Chest Pain	1	0.22
	10	2.22
Respiratory disorders		
Troubled Breathing	1	0.22
Cough	9	1.99
	10	2.22
Blood and lymphatic system disorders		
Anaemia	5	1.11
Pallor	1	0.22
	6	1.33

As per Naranjo's algorithm, out of 451 total reported ADRs, 82.93% ADRs were found to be possible while 17.07% ADRs were found to be probable. Since no re-challenge could be attempted due to ethical constraints, none could be attributed to be certain (Figure 3). According to WHO-UMC causality assessment scale, 78.05% (n=352) of the total ADRs were assessed as possible and 21.95% (n=99) were probable.

Severity assessment of the total reported adverse drug reactions were performed using Hartwig and Seigel's scale. Out of 451 reported ADRs, 88.47% ADRs were found to be mild, 11.09% ADRs were found to be moderate, while 2 were severe (Figure 4).

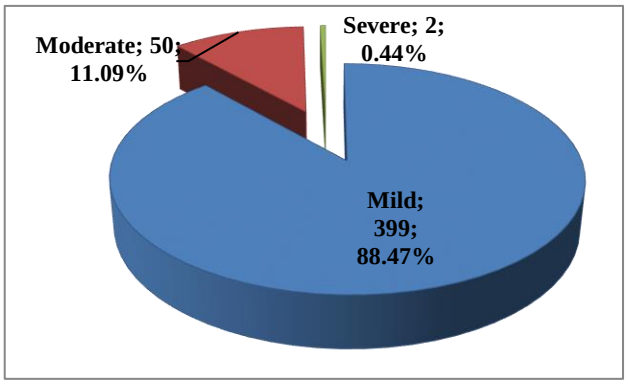

Figure 4: Severity assessment of the reported ADRs using Hartwig and Siegel's Scale.

DISCUSSION

Worldwide statistics states that an estimated 36.7 million people are living with human immunodeficiency virus (PLHIV), and around 46% of PLHIV were having access to antiretroviral therapy (ART) globally. The introduction of highly active antiretroviral therapy (HAART) have brought a ray of hope to PLHIV as it led to significant reduction in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality. The overall benefits of viral suppression and improved immune function as a result of effective antiretroviral therapy (ART) far outweigh the risks associated with the adverse effects of some antiretroviral (ARV) drugs. Rates of virological failure during first line regimens are decreasing both in clinical trials and in studies performed during routine clinical practice. However, drug-related adverse events and toxicities are increasingly recognized and represent one of the most common reasons for treatment discontinuation or switch. Generally, less than 10% of ART-naive patients enrolled in randomized trials have treatment-limiting adverse events. As ART is now recommended for all patients regardless of CD4 T lymphocyte (CD4) cell count, and therapy has to be continued indefinitely, the focus of patient management has evolved from identifying and managing early ARV-related toxicities to individualizing therapy to avoid long-term adverse effects. To achieve sustained viral suppression over a lifetime, both long-term and short-term

ART toxicities must be anticipated and overcome. The present study probed into the short term adverse effects of the first line regimen consisting of tenofovir, lamivudine and efavirenz.

The present study included a total of 242 PLHIV who were put on first line ART regimen comprising of tenofovir, lamivudine and efavirenz. Out of these 242 PLHIV put on TDF+3TC+EFV regimen, majority of the study population were males, with patients belonging to 31 to 40 years of age group representing the maximum study population. Out of total patients on the regimen, 75 patients did not encounter any adverse reactions during the entire study period. Out of remaining 167 patients, 83 patients encountered with one ADR, 57 patients with two ADRs and 27 patients with three or more ADRs.

Adverse drug reaction profile revealed that maximum ADRs were attributed to various psychiatric disorders which included insomnia, dizziness, drowsiness, headache, numbness, impaired concentration, mood swings. Dizziness, headache, drowsiness and insomnia were mostly common. CNS side-effects observed with efavirenz include dizziness, headache, confusion, stupor, impaired concentration, agitation, amnesia, depersonalization, hallucinations, insomnia, and abnormal or vivid dreams.[11-13] For most patients, these side-effects resolve within 6-10 weeks of starting treatment, but for some patients, symptoms seem to wax and wane long term. In pivotal clinical trials, more than 50% of patients taking efavirenz experienced some CNS effects, although few patients discontinued treatment as a result.[14] CNS disturbances were seen immediately after efavirenz treatment began. For most patients, these disturbances diminished or resolved within 2 months. Neither dose reduction nor dose splitting, shortened or reduced the intensity of symptoms.[13]

Various gastrointestinal disorders included anorexia, flatulence, nausea, vomiting, abdominal pain /cramps, diarrhoea, dyspepsia. GI complaints, mainly diarrhea, vomiting, and abdominal disturbances, were the most frequently observed ADRs in several studies. These types of ADRs appeared mainly during the first 12 weeks of therapy and were mild (grade $\leq$2) and transient in most patients. Gastroenterological intolerance (dyspepsia, nausea, vomiting, and diarrhea) is common effects of different drug combinations. Our study revealed that the major gastrointestinal complaint was nausea, followed by vomiting, diarrhoea, abdominal cramps respectively.

Antiretroviral drugs are not devoid of musculoskeletal complications. The mechanism by which antiretroviral drugs act on the bone is multifactorial and not completely clear but is mediated in part by a direct effect on osteoblasts and osteoclasts, increased catabolism of vitamin D, and mitochondrial damage. Interestingly, the mitochondrial damage can also cause proximal renal tubulopathy. Indeed, 1.6% to 22% of tenofovir-treated patients experience phosphate wasting and 1-hydroxylation defects of vitamin D due to proximal renal tubulopathy, leading to osteomalacia with multiple fractures, bone pain, and proximal muscle weakness.[15] Persistent or worsening bone pain, pain in extremities, fractures and/or muscular pain or weakness may be manifestations of proximal renal tubulopathy and should prompt an evaluation of renal function in at-risk patients. In the present study, generalized weakness, body ache and muscle cramps/pain were amongst various musculoskeletal disorders.

HIV-infected patients have a higher risk of developing cutaneous reactions than the general population [16], which has a significant impact on patients' current and future care options. The severity of cutaneous adverse reactions varies greatly, and some may be difficult to manage. HIV-infected patients at the beginning of the antiretroviral treatment can frequently show a wide variety of adverse drug effects such as drug rashes, hyperpigmentation, hair loss, hypersensitivity reactions, injection site reaction, urticarial reaction, erythema multiforme, toxic epidermal necrolysis (TEN) or Stevens–Johnson syndrome (SJS). Cutaneous adverse drug reactions have been reported with all antiretroviral medications. Therefore, it is necessary to develop and get approval of novel antiretrovirals as soon as possible in order to avoid these cutaneous adverse reactions. Our study showed that the major regimen induced dermatological complications presenting in our study set up included rashes, itching, SJS, pigmentation of nails, skin hyper pigmentation respectively. The morbilliform eruption, often referred to as a maculopapular rash, is the most common type of reaction after treatment. Nail and skin hyperpigmentation have been reported in long-standing patients infected with HIV. Hyperpigmentation can also be shown as a manifestation of photosensitivity in HIV-infected patients. It has been observed either related to or independent of the HAART therapy. Therefore, in patients with HIV infection, it is difficult to distinguish the reason for the aetiology of hyperpigmentation. These adverse effects resemble the dermatological effects of retinoids. Homologies between the amino acid sequences of retinoic acid-binding protein 1 and the catalytic site of HIV type-1 (HIV-1) proteases have been noted.[17] Moreover, drug-induced nail pigmentation typically involves several nails and is usually reversible. However, it may take several years to recover melanin production by melanocytes of the nail matrix after drug withdrawal.[18]

Besides the novel benefits of HAART, this treatment is also associated with undesirable metabolic complications ranging from insulin resistance, dyslipidemia, elevated diastolic blood pressure, visceral adiposity and/or peripheral lipoatrophy, elevated serum biomarkers for prothrombotic events, and chronic inflammation. Long term consequence of the metabolic complications of antiretroviral therapy on cardiovascular risk plays a major role in the management of HIV infection. Metabolic abnormalities like increased liver enzymes and lipid levels were noted in our set up.[19]

Patients treated with nucleoside analogue reverse transcriptase inhibitors (NRTIs) develop a varying degree of myopathy or neuropathy after long-term therapy. The tissue distribution of phosphorylases responsible for phosphorylation of NRTIs relates to their selective tissue toxicity. The NRTI-induced mitochondrial dysfunction has an influence on the clinical application of these agents, especially at high doses and when combined. Peripheral neuropathy and tremors were noted in our set up.[20]

The introduction of HAART regimens, by preventing opportunistic infections and reducing the incidence of myocarditis, has reduced the prevalence of HIV-associated cardiomyopathy of about 30% and the prevalence of cardiac involvement of AIDS-associated malignancies of about 50%. However, HAART regimens, especially those including protease inhibitors have been shown to cause, in a high proportion of HIV-infected patients, a metabolic syndrome (lipodystrophy/lipoatrophy, dyslipidemia, type 2 diabetes mellitus, insulin resistance) that may be associated with an increased risk of cardiovascular disease (approximately 1.4 cardiac events per 1000 years of therapy according to the Framingham score). A careful stratification of the cardiovascular risk and cardiovascular monitoring of patients under HAART according to the most recent clinical guidelines is needed.[21] However, our study did not encounter any severe cardiovascular complications. Mild complications like palpitation, moderate increase in blood pressure and chest pain were noted in our study.

The lung is the most common site of complications resulting from HIV infection. These respiratory conditions may be of infective or noninfective origin. Apart from the disease process, many antiretroviral drugs are also responsible for causing respiratory problems. In our set up, respiratory problems like cough and troubled breathing were noted in few patients.

Anaemia is associated with more advanced HIV disease, lower CD4 cell count, and higher viral load.[22] The advent of highly active antiretroviral therapy has reduced incidence of anaemia,it does remain an independent risk factor for death in people with HIV.[23] Drugs can cause anaemia by different mechanisms. All types of blood cells are produced in the bone marrow; drugs that damage the bone marrow can cause shortages in all of these cells. Among the antiretroviral drugs, zidovudine, is most often associated with bone marrow toxicity. Tenofovir based regimens are considered relatively safer in this regard. A case report has also suggested that anaemia can be a side-effect of efavirenz. Anaemia and pallor were rare.[24]

Our study had certain limitations also. Being an OPD based study, it is quite possible that some ADRs were missed that were transient or too mild to have inconvenienced the patient to report. Being a government set up, no detailed investigations could be ordered apart from routine laboratory investigations. Moreover the study was conducted for a short period at a single centre with a small sample size, thus the data cannot be a representative of national statistics. The study failed to identify the potential predictors of ADRs to ART in HIV infected patients. The study may not be a representative to true ADR detection rates as data is largely generated by spontaneous reporting system as proposed by PvPI. Risk factor correlation was not studied. Thus, presence of other confounding factors which could have affected the final outcome of the study which were beyond the scope of current study remains a faint possibility. Moreover, the study time period was much shorter for adjudging long term complications of this regimen. Thus only a trend towards aforesaid complications could be determined.

CONCLUSION

The study enables to obtain information on the pattern of adverse drug reactions associated with first-line regimen comprising of once daily dosing of tenofovir, lamivudine, efavirenz in treatment naïve PLHIV. Need of intensive monitoring for ADRs in ARTs and proper patient counseling regarding ADRs associated with a respective regimen should be made a mandatory part of the HIV care package so as to facilitate reporting and management.

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REFERENCES

1. International AISA Vaccine Initiative. Available at: https://www.iavi.org/how-to-help/learn/the-hiv-aids-pandemic . Accessed on Oct 24, 2016
2. HIV/AIDS. World Health Organization. Available at: http://www.who.int/gho/hiv/en/ Accessed on Oct 24, 2016
3. Lederman MM, Valdez H. Immune restoration with antiretroviral therapies: implications for clinical management. JAMA. 2000;284:223-8.
4. Chakraborty R. Infections and other causes of death in HIV-infected children in Africa. Paediatr Respir Rev. 2004;5:132-9
5. Candiani T, Pinto J, Cardoso CA, Carvalho IR, Dias A, Carneiro M, et al. Impact of highly active antiretroviral therapy (HAART) on the incidence of opportunistic infections, hospitalizations and mortality among children and adolescents living with HIV/AIDS in Belo Horizonte, Minas Gerais State, Brazil. Cadernos de Saúde Pública. 2007;23:S414-23.
6. Molina JM. Efficacy and safety of once-daily regimens in the treatment of HIV infection. Drugs. 2008;68(5):567-78.
7. Maek-A-Nantawat W, Avihingsanon A, Thainsanguankul W, Wongsabut J, Gorowara M, Ramautarsing R, et al. Safety and efficacy of once-daily single generic fixed-drug combination tablet of tenofovir, lamivudine and efavirenz among HIV-

infected Thais. Journal of the International AIDS Society, North America, 15, Nov. 2012.
8. Naranjo CA, Busto U, Sellers EM. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981 Aug;30(2):239-45.
9. The use of the WHO-UMC system for standardised case causality assessment. Available at: http://who-umc.org/Graphics/24734.pdf. Accessed on May 21, 2016.
10. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm. 1992 Sep;49(9):2229-32.
11. Colebunders R, Verdonck K. Reply to Gonzalez and Everall: Lest we forget: neuropsychiatry and the new generation anti HIV drugs. AIDS. 1999;13:869.
12. Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. New England Journal of Medicine. 1999 Dec 16;341(25):1865-73.
13. Moyle G. Efavirenz: practicalities, considerations and new issues. Int J Clin Pract Suppl. 1999;103:30-4.
14. SUSTIVATM (efavirenz) capsules, US Prescribing Information. Wilmington, DE: Du Pont Pharmaceuticals Company; 2000.
15. Fabbriciani G, De Socio GVL, Massarotti M. Antiretroviral Therapy and Adverse Skeletal Effects. Mayo Clinic Proceedings. 2011;86(9):916-7.
16. Hernandez-Salazar A, de Leon-Rosales SP, Rangel-Frausto S, Criollo E, Archer-Dubon C, Orozco-Topete R. Epidemiology of adverse cutaneous drug reactions. A prospective study in hospitalized patients. Archives of medical research. 2006 Oct 31;37(7):899-902.
17. Carr A, Samaras K, Chisholm DJ, Cooper DA. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. The Lancet. 1998 Jun 20;351(9119):1881-3.
18. Piraccini BM, Iorizzo M, Antonucci A, Tosti A. Drug-induced nail abnormalities. Expert opinion on drug safety. 2004 Jan 1;3(1):57-65.
19. Dau B, Holodniy M. The Relationship Between HIV Infection and Cardiovascular Disease. Current Cardiology Reviews. 2008;4(3):203-18.
20. Bennett GJ, Doyle T, Salvemini D. Mitotoxicity in distal symmetrical sensory peripheral neuropathies. Nature reviews Neurology. 2014;10(6):326-36.
21. Barbaro G. Reviewing the cardiovascular complications of HIV infection after the introduction of highly active antiretroviral therapy. Curr Drug Targets Cardiovasc Haematol Disord. 2005 Aug;5(4):337-43.
22. Wills TS, Leitz G, Nadler JP, Powers S, Somboonwit C, Vincent A, et al. Anaemia prevalence among HIV patients: antiretroviral therapy and other risk factors. InAntiviral Therapy 2003 Aug;8(4):L89-90.
23. Buskin SE, Ellis GM, Pepper GG, Frenkel LM, Pergam SA, Gottlieb GS, et al. Transmission Cluster of Multiclass Highly Drug-Resistant HIV-1 Among 9 Men Who Have Sex with men in seattle/king County, WA, 2005-2007. Journal of Acquired Immune Deficiency Syndromes (1999). 2008 Oct 1;49(2):205.
24. Freercks RJ, Mehta U, Stead DF, Meintjes GA. Haemolytic anaemia associated with efavirenz. Aids. 2006 May 12;20(8):1212-3.

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