Journal of Pharmacovigilance
ISSN: 2329-6887

Teklay et al., J Pharmacovigilance 2013, 1:4
DOI: 10.4172/2329-6887.1000115

Research Article Open Access

Adverse Effects and Regimen Switch among Patients on Antiretroviral Treatment in a Resource Limited Setting in Ethiopia

Gebrehiwot Teklay*, Befikadu Legesse and Mebratu Legesse
Department of Pharmacy, College of Health Sciences, Mekelle University, Mekelle, Ethiopia

Abstract

Background: Highly active antiretroviral therapy is the cornerstone of management of patients with human immunodeficiency virus infection. Antiretroviral therapy can prolong survival of patients however this drugs are associated with adverse effects that can affect patient adherence and if severe may require regimen change. The aim of the study is to assess the prevalence of antiretroviral associated adverse effects and management strategies undertaken among patients taking antiretroviral therapy in Jimma University Specialized Hospital.

Methods: A retrospective review of patient medical records (2009-2011) was done to assess adverse effects associated with antiretroviral therapy. A sample of 403 patient medical records was selected using systematic random sampling method. Data was collected using structured data abstraction format. Data were entered into SPSS windows version 16 and chi-square test was used to analyze factors associated with adverse effects. P-value of less than 0.05 was considered as statistical significant.

Results: About 65.5% of patients had developed at least one adverse effect to antiretroviral drugs. The most commonly encountered adverse effects were gastrointestinal and central nervous system effects. Severe side effects that resulted in high rate of regimen switch and discontinuation included anemia, peripheral neuropathy, rash and hepatotoxicity.

Conclusion: Majority of patients taking antiretroviral therapy experienced mild to severe adverse effects in the course of treatment which can affect the patient treatment outcome. Thus close monitoring of toxicities considering the risk-benefit ratio of continuing, switching or discontinuation of treatment is critical.

Keywords: Antiretroviral therapy; Side effects; Regimen switch; Management; Ethiopia

Abbreviations: ALT: Alanine Amino Transferase; ART: Antiretroviral Therapy; BMI: Body Mass Index; CD4: Cluster of Differentiation 4; CNS: Central Nervous System; DDI: Didanosine (*vidax®*); D4T: Stavudine (*zeri®*); EFV: Efavirenz (*sustiva®, strocrin®*); GI: Gastrointestinal; HAART: Highly Active Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; LPV/r: Lopinavir/ritonavir (*kaletra®*); NVP: Nevirapine (*viramune®*); PLWHA: People Living With HIV/AIDS; SPSS: Stastical Package For Social Sciences; TB: Tuberculosis; ZDV: Zidovudine (*retrovir®*); 3-TC-Lamuvudine, (*epivir®*); ZDV/3-TC-Zidovudine/Lamuvudine (*combivir®*); ZDV/3:TC/NVP: Zidovudine/Lamuvudine/Nevirapine (*zidolam®*)

Introduction

The Human immunodeficiency virus (HIV) infection has created enormous challenges worldwide since recognition of the disease. The highest number of people living with HIV/AIDS (PLWHA) is found in Sub Saharan Africa. Ethiopia is among those countries affected with the epidemic [1,2]. The overall growth of the epidemic has stabilized in recent years. Due to increase in people receiving antiretroviral therapy (ART) the number of AIDS-related deaths has declined [3]. People infected with the HIV are now living longer, healthier live. Since introduction of the ART, the disease has become in developing countries a chronic condition that can be managed for long term [3,4].

The combination ART is the corner stone of management of patients with HIV infection. Current ART regimens are capable of reducing viral load to undetectable levels, with a consequent increase in immune cells and reduction in development of opportunistic infections [4,5]. In recent years there is a growing awareness of the problems accompanying the use of HAART. In addition to drug resistance and difficulty of adhering to complex regimens, adverse effects associated with HAART have become a major concern [6]. Inspite of ART benefits, adverse effects to these drugs have been pointed as one of the main reasons for discontinuation, switch and non adherence [7-9].

Some clinical outcomes in AIDS patients are difficult to differentiate whether from the disease itself or from ART side effects. Neurologic complications occur in advanced AIDS disease and may be exacerbated by ART [10]. Anemia in HIV infected patients has multiple possible causes: HIV infection, drugs (zidovudine, cotrimoxazole, anti-tuberculosis), malnutrition, and blood loss [11]. Diarrhea in AIDS patients could be due to drug related or due to HIV invasion of the intestine resulting in enteropathy or due to gastrointestinal opportunistic infections [12]. Viral hepatitis coinfection and alcohol may increase the risk of adverse hepatic effects of ART [13]. Therefore, confounders to ART adverse effects may range from the clinical outcomes of the disease itself (advanced HIV infection) to immune reconstitution inflammatory response, concomitant medications, comorbidities and opportunistic infections.

Some studies reported high occurrence of antiretroviral adverse effects in Ethiopia HIV infected patients. In a study done by Feleke et al. the prevalence of lipodystrophy and hyperlipidemia was 68.3%,

***Corresponding author:** Gebrehiwot Teklay, Department of Pharmacy, College of Health Sciences, Mekelle University P.O.Box 1871, Mekelle, Ethiopia, Tel: 251910121281 E-mail: tgebrehiwet@gmail.com

Received June 04, 2013; **Accepted** December 16, 2013; **Published** December 24, 2013

Citation: Teklay G, Legesse B, Legesse M (2013) Adverse Effects and Regimen Switch among Patients on Antiretroviral Treatment in a Resource Limited Setting in Ethiopia. J Pharmacovigilance 1: 115. doi:10.4172/2329-6887.1000115

and 56.9% respectively [14]. Woldemedhin et al. found toxicity as the most common reason for ART regimen change [15]. Understanding the existing HIV treatment strategy is important to assure the efficacy and safety of antiretroviral treatment so as to improve patient adherence and quality of life. The study aimed to assess the prevalence of antiretroviral associated adverse effects and management strategies undertaken among patients taking ART in Jimma University Specialized Hospital.

Methods

A cross-sectional study was conducted by a retrospective review of three years' (2009-2011) patient medical records at the ART clinic of Jimma University Specialized Hospital. Data was collected from February to March, 2012.

Patient medical records were used for abstracting information about patients' socio-demography, adverse effects, regimen switch and interruption of treatment. The source population was all HIV patients who started ART and on follow up in the clinic and patients who had more than six month of follow up in the clinic was included in the study.

The sample size was determined using the single population proportion formula, assuming the prevalence of ART adverse effects to be 50%, and 5% margin of error at 95% confidence interval. After considering a 5% increment for non-response, the sample size was determined to be 403.These records were drown from the source population by systematic random sampling, using the list of the card numbers as sampling frame. The sampling interval (k) was determined by dividing the total source population by the sample size (3400/403=8). The first medical record was selected randomly from the first eight records in the sampling frame and then every eighth record was included in the study.

A pre-tested structured data abstraction format was used for data collection. Official letter was written to the hospital medical director from Jimma University. Patient information was kept confidential. The data was collected by trained Nurses under the supervision of the principal investigator. After all data was obtained, it was checked for completeness and clarity. A particular patient record with missed data was excluded

Regimen type	Adverse effects	Frequency (%)
Efavirenz-based (n=214)	Nightmare Insomnia Headache Dizziness GI*, total Rash	67(54.0) 45(36.0) 65(52.4) 38(30.6) 35(28.0) 25(20.1)
Nevirapine based (n=304)	Rash Hepatotoxicity Headache Nausea	87(26.0) 27(8.0) 27(8.0) 20(6.0)
Zidovudine based (n=131)	Anemia Fatigue Headache GI total Dizziness Insomnia Cough Lipodystrophy	21(26.6) 49(62.0) 45(56.9) 35(44.3) 25(31.6) 43(54.4) 28(35.4) 2(2.5)
Stavudine based (n=364)	Peripheral neuropathy Headache Dizziness Insomnia Nausea and vomiting Lipodystrophy	75(21.5) 92(26.4) 52(14.9) 51(14.6) 55(15.7) 5(1.4)
Protease inhibitor based (n=1)	Nausea and vomiting Peripheral neuropathy	1(100.0) 1(100.0)

*GI=Gastrointestinal

Table 1: Regimen-based prevalence of major adverse effects associated with ART.

Data were entered, coded and analyzed using SPSS for windows version 16 statistical software. Descriptive statistical analysis was used to describe patient demographics, clinical and laboratory characteristics and ART regimens. Since all variables were categorical chi-square test was used to analyze factors associated with increased occurrence of adverse effects. P-value of less than 0.05 was considered as statistical significant.

Operational Definitions

Tuberculosis treatment interaction

Interaction antiretroviral therapy with treatment of TB (mainly nevirapine and rifampcin), reducing the efficacy of anti-retroviral drugs and of anti-TB drugs while increasing the risk of drug toxicity.

Toxicity

Severe and life threatening adverse effect to ARV drugs in a dose normally used for treatment and requiring change in therapy.

Results

Four hundred three (403) patient records were reviewed in the study. Patient demographic characteristics showed that 264 (65.5%) patients were females and 139 (34.5%) males. Majority of the patients, 376 (93.3%) were in the age group of 15-49 years. Regarding patient source, most of them (96%) were outpatients and 16 (4%) had history of hospitalization. Fourteen (5.3%) of the females had history of pregnancy. The nutritional status of patients was estimated using body mass index (BMI) considering the weight and height at the start of treatment. One hundred seventy one (42.4%) had BMI less than 17 and 98 (33.3%) and 134 (24.3%) had BMI 17-18 and greater than 18, respectively. Regarding the CD4 counts at the start of ART, 299 (74.2%) patients had CD4 count less than 200cells/mm^3.

The most commonly prescribed initial antiretroviral regimens were D4T (30)/3-TC/NVP in 55% of patients; followed by ZDV/3-TC/NVP, D4T(30)/3-TC/EFV, D4T(40)/3-TC/NVP, D4T(40)/3-TC/EFV, ZDV/3-TC/EFV in 12.6, 11.9, 11.5, 4.5 and 4.5%, respectively. ART switch occurred in 136 (37.7%) patients where almost all of this switches were within the first line drugs. Only in one patient a second line protease inhibitor based regimen (D4T/DDI/LPV/r) was used due to treatment failure to the first line stavudine based regimen.

Out of the 403 patient records reviewed 264 (65.5%) patients had at least one adverse effect related to the antiretroviral treatment. Two hundred three (50.3%) patients had a recorded history of three or more adverse effects. Mild but commonly encountered adverse effects were gastrointestinal; nausea (28%), vomiting (23.8%) diarrhea (20.6%); and central nervous system (CNS) side effects: nightmare (24.6%), dizziness (15.6%) and insomnia (20.5%). Moderate to severe adverse effects recorded were anemia characterized by hemoglobin less than 11mg/dl and fatigue in 81 (20.1%), peripheral neuropathy in 91 (22.7%), hepatotoxicity characterized by elevated liver enzyme and jaundice in 37 (9.2%), and rash in 121 (30%). Six patients reported a very severe rash. Some 79 (19.7%) patients had recorded history of cough which was difficult to identify it as drug or disease related. The rarely observed side effect was body fat accumulation (lipodystrophy) in 7 (2%) patients. Table 1 and Figure 1 shows regimen based prevalence of major adverse effects. High frequency of regimen discontinuation and switch

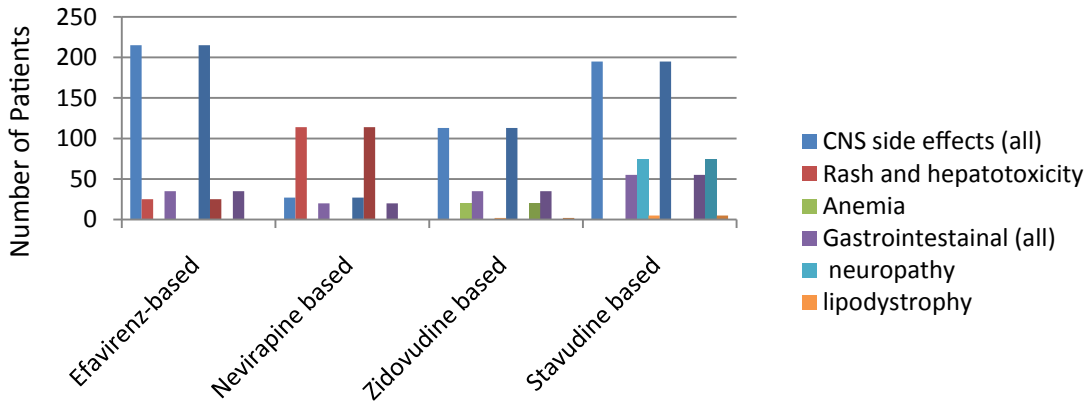

Figure 1: Regimen-based prevalence of major adverse effects associated with ART.

was observed in patients who experienced anemia, rash, hepatotoxicity, and peripheral neuropathy.

When we see the time occurrence of adverse effects, rash hepatotoxicity, most GI, and CNS adverse effects occurred early after starting treatment at mean interval of 2 weeks. Lipodystrophy, anemia, and peripheral neuropathy were among the long term adverse effects observed with mean time occurrence of 2, 1.6, and 0.5 years respectively. One hundred forty (34.7%) patients had co-morbid tuberculosis and 43 patients changed previous ART regimen due to Nevirapine drug interaction with antituberculosis drugs. About 303 (75%), and 108 (27%) patients were on cotrimoxazole and isoniazid prophylaxis, respectively.

ART switch was done in about 257 (62.8%) patients while 27 patients switched two times during the three years of duration. The main reason for ART switch was weight gain (129 (50.2%) patients); where patients previously on 30 mg stavudine had to switch to 40mg when the patients' weight is above 60 kg. Patients who switched to 40 mg stavudine reported more adverse effects such as peripheral neuropathy. The other reasons for ART switch was toxicity (30%), tuberculosis treatment interaction (17.1%), pregnancy (3.3%) and treatment failure (0.38%).

Regarding the clinical measures taken to manage the adverse effects, 77 patients switched to other regimen (20 of them discounted treatment for days and switched later) while 10, 22, and 12 patients were made to discontinue the concomitant anti-tuberculosis, isoniazid and cotrimoxazole prophylaxisis, respectively. Supportive medications prescribed for management of adverse effects were amitriptyline, diclophenac, diphenhydramine, iron sulfate, predinisolone, methclopropamide, cemetidine and metronidazole. Except metronidazol, which was used for treatment amebiasis infection, the supportive medications were given for management of the adverse effects. Amitriptyline –peripheral neuropathy; iron sulfate for anemia; predinisolone for rash; methclopropamide and cemetidine for mangment of gastrointestinal events.

Table 2 summarizes the association of variables with occurrence of adverse effects. Variables found with clinically significant association were age, body mass index, CD4 count, regimen type, ART switch and presence of concurrent drug.

Discussion

Effective treatment of HIV infection requires a minimum of three drug regimen which could be complicated and commonly associated with adverse effects. In this study, the prevalence of adverse effect was about 65.5%. A higher prevalence of adverse effects (92.2%) was reported from a study in Brazil [9]. This difference could be due to differences in methodology, where the study in Brazil was based on patient self report and our study was based on patient records which could be affected by adverse effect recording and reporting practice of the health professionals. Similar to a study conducted in two public referral HIV/AIDS centers in Brazil [8], the most commonly encountered side effects were gastrointestinal and CNS side effects. Other common but more severe adverse effects were rash, peripheral neuropathy, anemia and hepatotoxicity.

Parallel to findings from pivotal trials [16], CNS side effects were common among patients on efavirenz based regimens (D4T/3TC/EFV, ZDV/3TC/EFV). Though studies on pharmacogenomics data of Ethiopians are lacking, some reported variability in the CYP2B6*6/*6 and ABCB13435TT genotype are common in Ethiopians resulting in elevated plasma efavirenz and increased side effects [17]. As compared to EFV based regimen, patients on NVP based regimen experienced higher rates of hypersensitivity reactions (rash, hepatotoxicity). Very severe rash, which seems Steven Johnson Syndrome (SJS), occurred in seven patients on NVP and cotrimoxazole; it was difficult to identify which drug caused this syndrome. Slightly higher rate of efavirenz associated hepatotoxicity (12.5%) was observed in a prospective cohort study by Maggiolo et al. [18]. High occurrence of hepatotoxicity was significantly associated with long duration of use, higher hepatitis virus coinfection, and high baseline Alanine amino transferase (ALT). In our case, though no record of hepatitis virus coinfection was found, the high rate of hepatotoxicity and rash could be due to overlapping toxicities with anti-tuberculosis drugs. Patients on antituberculosis were at higher risk of developing adverse effects as compared to patients on cotrimoxazole (OR=4, CI, 0.12-1.7, p=0.04). Such overlapping toxicities could be serious and challenging in the management of patients with TB-HIV co-infection.

Stavudine (D4T) based regimens were the commonly used regimens in our setting despite occurrence of adverse effects like peripheral neuropathy (21.5%), lipodystrophy (1.4%) and some gastrointestinal events. A study from an outpatient clinic in Kenya also reported peripheral neuropathy (20.7%) as most commonly encountered side effect [19]. More peripheral neuropathy was reported in patients who switched from D4T (30) to D4T (40) due to weight gain [19-21].

Variables		Adverse effect			OR(95% CI) p-value
		Yes (No, %)	No (No, %)	Total	
Age (yr)	<15 15-50 >50 Total	2(15.4) 249(66.2) 13(92.8) 264	11(84.6) 127(33.7) 1(7.1) 139	13 376 14 403	1 2.528 (1.422 4.496, p=0.4) 3.84 (0.48-30.47,p=0.006*)
Sex	Male Female Total	92(66.2) 172(65.2) 264	47(33.8) 92(34.8) 139	139 264 403	1 4.95 (0.63-38.94,p=0.8)
BMI****(kg/m^2)**	>18 <18 Total	67(50) 197(73.1) 264	67(50) 72(26.8) 139	134 269 403	1 1.94 (1.087-3.49)p=0.03*)
Regimen type	D4T (30)/3-TC/NVP D4T(40)/3-TC/NVP D4T(30)/3-TC/EFV D4T(40)/3-TC/EFV ZDV/3-TC/NVP ZDV/3-TC/EFV D4T/DDI/LPV/r Total	135(57.7) 121(72.9) 50(60.2) 49(72.9) 45(66.2) 40(63.5) 1(100) 441	99(42.3) 45(27.1) 33(39.8) 19(28) 23(33.8) 23(36.8) 0	234 166 83 68 68 63 1	1 1.86 (1.01-3.44,p=0.04*) 0.36 (0.08-1.59), p=0.18) 0.76 (0.23-2.55), p=0.66 0.19 (0.01-3.2), p=0.25 2.1 (0.26-17.3), p=0.49
CD4 count (cells/ mm^3)	<200 200-400 >400 Total	53(43.4) 125(83.3) 86(65.6) 264	69(56.6) 25(16.7) 45(34.4) 139	122 150 131 403	1 1.8 (0.62-5.2), p=0.27 5.71 (1.32-24.6), p=0.00*
Adherence	Good Poor Total	261(65.5) 3(75) 264	138 (34.5) 1(25)	399 4 403	1 1.5 (0.59-33.79), p=0.17
ART switch	Yes No Total	175(69) 89(59) 264	78(31) 61(41)	253 150 403	1 3.75 (0.77-18.17), p=0.04*
Concurrent drugs	Cotrimoxazole Isoniazid Anti-tuberculosis Anti-fungal Total	256(66.8) 67(62) 72(60) 21(55.3) 436	127(33.2) 41(38) 48(40) 17(44.7)	383 108 120 38 649	1 1.65 (0.56-4.87),p=0.36 4 (0.12-1.7), p=0.04* 2.115 (1.111-4.027, p=0.51

* P<0.05, statistically significant association; **BMI=Body Mass index.

Table 2: Factors associated with occurrence of adverse effects among patients on ART.

Unlike to low rate of ZDV induced anemia (12%) reported from tertiary general hospital, in London, anemia was significant in our study (26.6%). Underweight might be the reasons behind in our study subjects where underweight patients were 1.96 times more to develop adverse effects [15].

In contrast to other studies [8,19] there were no sex difference in rate and severity of adverse effects. Variables statistically associated with occurrence of adverse effects were age>60, body mass index <18, CD4 count >400, regimen on D4T(40)/3-TC/NVP, ART switch and presence of concurrent antituberculosis drugs. Related study by Menezes [8] found sex, ART switch, and high CD4 count as predictor of ART toxicity. Age older than 40 years was independent predictor of clinical toxicity in another study conducted in outpatient clinic [19]. CD4 count in this study indicates improved therapeutic outcome since many patients had increment in CD4 counts as compared to baseline. Patients with CD4 count 200-400 had higher occurrence of adverse effects, though no significant difference was obtained in this study, many studies report that female patients with high CD4 count (>250 cells/mm^3) are at high risk of Nevirapine associated rash and hepatotoxicity [22]. Currently there is increasing interest that genetic variability can significantly affect individuals' response adverse effects. In Ethiopian population pharmacogenomic data of antiretrovirals are lacking and this limits us to explain the existing difference in response to ART medication between Ethiopians and other population across the world.

In this study the clinical measures undertaken to manage adverse effects were ART switching, discontinuation of co-medications and prescribing supportive medications. Adverse effects that required high rate of regimen switch were rash, anemia, peripheral neuropathy and hepatotoxicity. Similarly, studies found that hypersensitivity (rash and hepatitis), hematologic and liver function abnormalities were common toxic effects leading to change in ART [19,23].

Many studies reported toxicity as the main reason for ART switch [18,19,21]. In this study the main reason for ART switch was weight gain followed by toxicity and TB treatment interaction. Likewise, in a study in Kenya the ART related toxicity and tuberculosis treatment interaction were the main reasons for ART switch [19]. ART switch by itself may result in development of new and severe side effects and further complications and loss of future treatment options.

Some of the limitation of the study was poor adverse effect recording and reporting by the health professionals. Some effects of the ARV drugs are also found in people with HIV infection which are characteristics advanced HIV infection, or might be related to concomitant medications and comorbidities). Being a retrospective study differentiation of ART adverse effect from AIDS related outcome was difficult. However AIDS related outcomes occur commonly in untreated patients or at early stage of treatment. The adverse effects are likely due to ART where there was strong temporal relationship of occurrence after initiating ART, pharmacologically related, and there was improvement up on discontinuation and switch to other agents.

Conclusion

In this study the prevalence of adverse effects associated with antiretroviral treatment were found common (65.5%). Mild but

commonly reported adverse effects were gastrointestinal and CNS adverse effects while anemia, peripheral neuropathy, rash and hepatotoxicity were severe effects resulted in high rate of regimen switch. ART switch could be an option for management of toxicities but it should be undertaken considering the risk of loss of future treatment options. Therapeutic drug monitoring may not be feasible in resource limited setting; therefore health providers working in the ART clinic should monitor patients both clinically and with laboratory for the occurrence of side effects. Particularly patients on ZDV, NVP and those on concomitant medication need close follow up. The health system should develop ADR database so as to easily record and report adverse effect.

Conflict of Interest

The authors declare no conflict of interest.

Authors' contributions

Mr. Gebrehiwot Teklay and Mr. Befikadu Legesse have great role in the study design and development of the proposal, data collection supervision, analysis and interpretation of data.

Mr. Mebratu Legesse has been involved in commenting the findings.

Mr. Gebrehiwot Teklay has developed the manuscript for evaluation and possible publication.

Acknowledgment

The authors would like to thank Jimma University Office of Research and community based education for the financial assistance and we are also thankful to the staff members of ART clinic for their kind cooperation during the data collection.

References

1. Joint United Nations Programme on HIV/AIDS (UNAIDS) (2005) AIDS epidemic update. WHO, Geneva.
2. Ethiopia Demographic and Health Survey (2011) Central Statistical Agency.
3. UNAIDS (2011) Unite for universal access: Overview brochure on 2011 high level meeting on AIDS.
4. TB/HIV A Clinical Manual (2004) TB/HIV A Clinical Manual. (2ndedn), World Health Organization (WHO), Geneva.
5. Bertram G (2011) Antiretroviral agents: Katzung Basic and clinical pharmacology. (11thedn), McGraw Hill Medical, New York.
6. Liz Highleyman (2000) Adverse effects associated with antiretroviral therapy. Bulletin of experimental treatment for AIDS, San Francisco AIDS foundation.
7. Kanmaz J (2000) Significant toxicities associated with antiretroviral therapy. Journal of pharmacy practice 13: 457-473.
8. Menezes de Pádua CA, César CC, Bonolo PF, Acurcio FA, Guimarães MD (2006) High incidence of adverse reactions to initial antiretroviral therapy in Brazil. Braz J Med Biol Res 39: 495-505.
9. Pádua CA, César CC, Bonolo PF, Acurcio FA, Guimarães MD (2007) Self reported adverse reactions among patients initiating antiretroviral in Brazil. Braz J Infect Dis 11: 20-26.
10. Gonzalez-Duarte A, Robinson-Papp J, Simpson DM (2008) Diagnosis and management of HIV-associated neuropathy. Neurol Clin 26: 821-832.
11. J Opie (2010) Haematological complications of HIV infection. S Afr Med J 102: 465-468.
12. Knox TA, Spiegelman D, Skinner SC, Gorbach S (2000) Diarrhea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection. Am J Gastroenterol 95: 3482-3489.
13. den Brinker M, Wit FW, Wertheim-van Dillen PM, Jurriaans S, Weel J, et al. (2000) Hepatitis B and C virus co-infection and the risk of hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. AIDS 14: 2893-2902.
14. Feleke Y, Fekadu D, Mezegebu Y (2012) Prevalence of highly active antiretroviral therapy associated metabolic abnormalities and lipodystrophy in HIV infected patients. Ethiop Med J 50: 221-230.
15. Woldemedhin B, Wabe NT (2012) The reason for regimen change among HIV/AIDS patients initiated on first line highly active antiretroviral therapy in southern Ethiopia. N Am J Med Sci 4: 19-23.
16. Treisman GJ, Kaplin AI (2002) Neurologic and psychiatric complications of antiretroviral agents. AIDS 16: 1201-1215.
17. Yimer G, Ueda N, Habtewold A, Amogne W, Suda A, et al. (2011) Pharmacogenetic & pharmacokinetic biomarker for efavirenz based ARV and rifampicin based anti-TB drug induced liver injury in TB-HIV infected patients. PLoS One 6: e27810.
18. Maggiolo F, Arici C, Airoldi M, Ripamonti D, Quinzan G, et al. (2007) Reasons for discontinuation of nevirapine containing HAART. J Antimicrob Chemother 59: 569-572.
19. Hawkins C, Achenbach C, Fryda W, Ngare D, Murphy R (2007) Antiretroviral durability and tolerability in HIV-infected adults living in urban Kenya. J Acquir Immune Defic Syndr 45: 304-310.
20. Sheneberger R, Edozien A, Fielder J, et al. (2007) ARV-associated drug toxicities leading to a switch in medication: experience in Uganda, Kenya and Zambia (Abstract 789). 14th conference on Retrovirus and Opportunistic Infection, Los Angeles.
21. Forna F, Moore D, Mermin J, Brooks JT, Were W, et al. (2009) Hematologic changes associated with Zidovudine following single-drug substitution from stavudine in a home-based AIDS care program in rural Uganda. J Int Assoc Physicians AIDS Care (Chic) 8: 128-138.
22. Shah J (2006) Adverse effects of antiretroviral therapy in HIV-1 infected children. J Trop Pediatr 52: 244-248.
23. Cozzi-Lepri A, Phillips AN, d'Arminio Monforte A, Piersantelli N, Orani A, et al. (2002) Virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with 2 nucleoside analogues in the Italian Cohort Naive Antiretrovirals (I.Co.N.A.) study. J Infect Dis 185: 1062-1069.