Jpn. J. Infect. Dis., 61, 205-209, 2008

Original Article

Immune Reconstitution Inflammatory Syndrome among HIV/AIDS Patients during Highly Active Antiretroviral Therapy in Addis Ababa, Ethiopia

Kahsay Huruy*, Andargachew Mulu[1], Getahun Mengistu[2], Aster Shewa-Amare[3], Addis Akalu[3], Afework Kassu[1], Gashaw Andargie[4], Daniel Elias[1] and Workineh Torben[5,6]

Department of Medical Laboratory Technology, [1]Department of Microbiology and Parasitology and [4]School of Public Health, College of Medicine and Health Sciences, University of Gondar, Gondar; [2]Department of Neurology, Faculty of Medicine and [5]Aklilu Lemma Institute of Pathobiology, Addis Ababa University; [3]Zewditu Memorial Hospital, Addis Ababa, Ethiopia; and [6]Texas Tech University Health Sciences Center, School of Medicine, Microbiology and Immunology, Texas, USA

(Received January 30, 2008. Accepted March 31, 2008)

SUMMARY: Suppression of viral replication is followed by increases in $CD4^+$ lymphocytes, and this has been shown to result in decreased susceptibility to opportunists after initiation of highly active antiretroviral therapy (HAART). However, clinical aggravations after the initiation of HAART have been thought to be due to the restored ability to mount an inflammatory response, or the immune reconstitution inflammatory syndrome (IRIS). The degree of IRIS observed in human immunodeficiency virus (HIV)-infected patients following initiation of HAART is variable. This prospective study was aimed at determining the proportion of IRIS and the pattern of opportunistic infections among 186 HIV/AIDS patients receiving HAART between December 2006 and July 2007 at Zewditu Memorial Hospital, Addis Ababa, Ethiopia. The proportion of IRIS was 17.2% (32/186). The mean number of days of IRIS occurrence for each disease ranged from 26 to 122 days with a mean of 80. Opportunistic diseases associated with IRIS were tuberculosis (68.8%, 22/32), herpes zoster rash (12.5%, 4/32), cryptococcosis (9.4%, 3/32), toxoplasmosis (6.3%, 2/32) and bacterial pneumonia (3.1%, 1/32). Compared to baseline readings there were significant increases in CD4 count, aspartate aminotransferase and alanine aminotransferase levels while hemoglobin values decreased during the development of IRIS. In summary, the proportion of IRIS and the pattern of opportunistic infections in HAART-treated patients in Ethiopia mirrored those reported in other countries. Further prospective surveys on epidemiological, immunological, microbial and clinical studies are imperative to assess the proportion and pattern of IRIS and effect of HAART in Ethiopia.

INTRODUCTION

Successful suppression of viral replications followed by an increase in $CD4^+$ lymphocytes, a partial recovery of T-cell specific immune responses and decreased susceptibility to opportunistic pathogens is usually observed after highly active antiretroviral therapy (HAART). However, some patients experience clinical deteriorations following initiation of HAART, which is believed to be a consequence of the restored ability to mount an inflammatory response. This phenomenon has been termed "immune reconstitution inflammatory syndrome" (IRIS) (1). IRIS describes a collection of inflammatory disorders associated with paradoxical worsening of preexisting infectious processes following the initiation of HAART in human immunodeficiency virus (HIV)-infected patients. Preexisting infections in individuals with IRIS may have been previously diagnosed and treated or they may be subclinical and later unmasked by the host's regained capacity to mount an inflammatory response (2,3).

The degree of immune reconstitution observed in HIV-1-infected patients following initiation of antiretroviral therapy (ART) is variable (4). A study done in Ohio found incidence rates of IRIS as low as 10% and as high as 25% (1). A similar rate of IRIS was also reported from London by Ratnam et al. (5). IRIS has been reported in association with a number of diseases and inflammatory conditions. These include tuberculosis (TB), herpes zoster (shingles), *Cryptococcus neoformans*, Kaposi's sarcoma (KS), *Pneumocystis* pneumonia, *Mycobacterium avium* complex (MAC), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex virus (HSV), *Histoplasma capsulatum*, human papillomavirus (HPV) and cytomegalovirus (CMV) (6). In many cases, IRIS may be mild and resolves without treatment. Deaths, however, have been reported, particularly in cases in which there is infection with *Cryptococcus* or *Mycobacterium* spp. (1). In addition, abnormalities in hepatic function have been shown to be one of the most common complications occurring among patients receiving HAART. Liver problems were found to be an important cause of morbidity and mortality in HIV patients, and the risk of toxicity was reported in the first 6 weeks of treatment (7).

As an effort made to control the epidemic of HIV, the Ethiopian government has recently developed a national policy on HIV/AIDS to guide implementation of successful programs including the provision of HAART. As a result, ART has officially been started since 2004 in the country. However, there is a public health fear that, despite the major beneficial effects in restoration of pathogen-specific immune responses, ART may lead to IRIS in which subclinical or existing infections occur with a paradoxical deterioration in association with recovery of the immune function. There is no documented data on IRIS in Ethiopia; therefore, this study was conducted to determine the proportion and pattern of IRIS

*Corresponding author: Mailing address: Department of Medical Laboratory Technology, College of Medicine and Health Sciences, University of Gondar, P.O. Box 196, Gondar, Ethiopia. Tel: +251-911771518, E-mail: kasaye88@yahoo.com

among HIV/AIDS patients receiving HAART at Zewditu Memorial Hospital, Addis Ababa.

METHODS

Study design, site and period: A prospective study was conducted at Zewditu Memorial Hospital, Addis Ababa between December, 2006 and July, 2007 to determine the proportion and risk factors of IRIS among HIV/AIDS patients after commencing HAART. Zewditu Memorial Hospital is a referral hospital that has a separate ART clinic established in July, 2003 and was the first ART clinic in Ethiopia. IRIS is defined as a phenomenon whereby an HIV/AIDS patient on antiretroviral treatment shows an increase in CD4 count, and manifests clinical illness due to infection by microorganisms (8).

Study subjects: The study subjects were HIV/AIDS patients who visited the hospital to start HAART. Since an expected 10% of HIV/AIDS patients with HAART in developing countries, at the very least, are expected to develop IRIS (5), and given the statistical requirements of a 95% confidence interval, a 5% margin of error and a 5% loss to follow up, a minimum of 145 subjects were planned to be enrolled. However, all HIV/AIDS patients who came to the ART clinic of the hospital seeking treatment during the data collection time were included. As a result, 186 total subjects were involved in the study.

Demographic and clinical data: A pre-designed structured questionnaire was used to collect socio-demographic characteristics and relevant clinical data of the patients (previous and current clinical data), and information related to risk factors for acquiring IRIS.

Nutritional assessment: Anthropometrics measurement, which is a proxy for nutritional assessment, was done for each study subject following World Health Organization (WHO) guidelines (9). Body weight was determined to the nearest 0.1 kg on a digital scale and height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated and used to determine the nutritional status of the study subjects, who were categorized as severe malnutrition (BMI < 15.9 kg/m^2), moderate malnutrition (BMI = 16 - 16.9 kg/m^2), mild malnutrition (BMI = 17 - 18.4 kg/m^2), normal (BMI = 18.5 - 24.9 kg/m^2), overweight (BMI = 25 - 29.9 kg/m^2) and obese (BMI > 30 kg/m^2) (9).

Blood collection and processing: About 5 ml of venous blood was collected in Vacutainer® tubes and divided into two aliquots: one was poured into test tubes containing EDTA and used for hematological and immunological investigations and the other was poured into a plain test tube to separate serum for liver function tests (10).

Laboratory investigations: Sputum was collected on follow-up from patients with clinical features suggestive of TB and examined by an acid-fast stain (AFS) technique to detect the presence of acid-fast bacilli (AFB). In addition, TB diagnoses were also made by chest X-ray and/or ultrasonic and histological examinations. Cerebrospinal fluid was examined microscopically for the detection of the cryptococcal capsule using India ink following the standard procedure. Toxoplasmosis was diagnosed using clinical features, CT scan with ring-enhancing lesions and therapeutic responses in combination.

Stool examinations were done by direct saline/iodine microscopic techniques following the standard procedure (9). Hemoglobin was determined using Haemo-analyzer (Abbott Laboratories, North Chicago, Ill., USA) following the manufacturer's protocol, and classifications of anemia were made based on the WHO guidelines (11). Measurements of CD4 and CD8 were also done using FACScount (Becton Dickinson, Sparks, Md., USA) following the manufacturer's instructions. Determination of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities was performed following standard protocols.

Ethical issues: The study was conducted after obtaining institutional and national ethical clearance. Informed consent was also obtained from the study subjects. Patients with IRIS were treated following standard protocols.

Statistical analyses: Data were entered and analyzed by SPSS version 13 statistical software (SPSS, Chicago, Ill., USA). Binary logistic regression analysis and students *t* test were performed. *P* values were determined and considered significant when found <0.05.

RESULTS

This prospective study was done to determine the proportion of IRIS and pattern of opportunistic infections (OIs) associated with IRIS after initiation of HAART in 186 HIV/AIDS patients. Most of the subjects (61/186, 33%) were in the age group 28 - 32 years followed by the age group 33 - 37 years (33/186, 17.7%). Most of the participants (111/186, 59.9%) were females. The majority of subjects were married (62/186, 33.3%) followed by single (54/186, 29%), widowed (52/186, 28%) and divorced (18/186, 9.7%).

As indicated in Table 1, the majority of the HIV/AIDS patients had a history of previous OIs. The predominant OIs observed in the patients were herpes zoster rash (43%) followed by TB (31.4%) and oral candidiasis (16.4%). Mixed OIs had also been observed in certain HIV/AIDS patients. The clinical findings regarding OIs at the time of HAART initiation revealed that 8 (29.6%) had TB, 14 (51.9%) had oral candidiasis, 1 (3.7%) had toxoplasmosis, 1 (3.7%) had *Pneumocystis* pneumonia, and 3 (11.1%) had herpes zoster rash. Among the 27 patients who had previous OIs, 6 developed IRIS; among 8 with active TB, 2 developed IRIS in

Table 1. Pattern of opportunistic infections among HIV/AIDS patients, Zewditu Memorial Hospital, Addis Ababa, Ethiopia

Opportunistic infection	Frequency (%)
Pattern of previous OIs	
Herpes zoster	37 (43.0)
Tuberculosis	27 (31.4)
Oral candidiasis	14 (16.4)
Tuberculosis and toxoplasmosis	2 (2.3)
Tuberculosis and herpes zoster	2 (2.3)
Pneumocystis pneumonia	2 (2.3)
Toxoplasmosis	1 (1.15)
Tuberculosis and oral candidiasis	1 (1.15)
Total	86 (100.0)
Pattern of OIs at time of HAART initiation	
Oral candidiasis	14 (51.9)
Tuberculosis	8 (29.6)
Herpes zoster	3 (11.1)
Toxoplasmosis	1 (3.7)
Pneumocystis pneumonia	1 (3.7)
Total	27 (100.0)

OI, opportunistic infection; HAART, highly active antiretroviral therapy.

Table 2. Characteristics of patients with and without immune reconstitution inflammatory syndrome events before and after initiation of HAART, Zewditu Memorial Hospital, Addis Ababa, Ethiopia

Variable	Patients with IRIS			Patients without IRIS		
	Baseline (Mean ± SD)	At time of IRIS (Mean ± SD)	*P*	Baseline (Mean ± SD)	After 24 weeks (Mean ± SD)	*P*
CD4 cell	104 (66.5)	196 (123)	0.001	127.5 (743.5)	214 (109.1)	0.001
AST	37.8 (23.2)	102.4 (119.4)	0.008	40.0 (29.5)	33.0 (31.3)	0.001
ALT	32.2 (22.1)	86.5 (109.6)	0.020	37.1 (37.9)	41.3 (35.6)	0.001
Hgb	10.7 (2.3)	9.3 (1.6)	0.002	12.4 (2.5)	–	–
BMI	18.6 (2.19)	18.4 (4.41)	0.827		–	–

IRIS, immune reconstitution inflammatory syndrome; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Hgb, hemoglobin; BMI, body mass index.

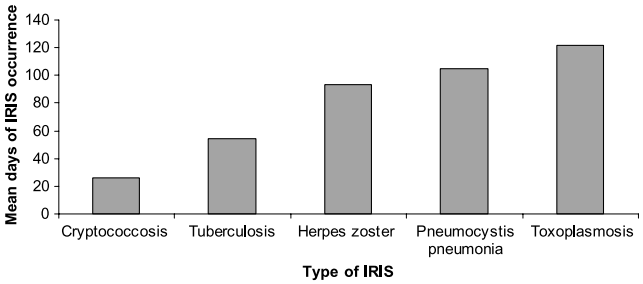

Fig. 1. Occurrence of immune reconstitution inflammatory syndrome (IRIS) after initiation of highly active antiretroviral therapy.

Table 3. Patterns of opportunistic infections after development of immune reconstitution inflammatory syndrome among HIV/AIDS patients, Zewditu Memorial Hospital, Addis Ababa, Ethiopia

Opportunistic infection type	No. (%)
PTB	10 (31.2)
EPTB	8 (25.0)
DTB	4 (12.5)
Herpes zoster	4 (12.5)
Cryptococcosis	3 (9.4)
Toxoplasmosis and hepatitis[1)]	2 (6.3)
Pneumocystis pneumonia	1 (3.1)
Total	32 (100.0)
Stool result	
Negative	15 (62.5)
Strongyloides stercoralis	4 (16.7)
Entamoeba histolytica/*dispar*	3 (12.5)
Giardia lamblia	2 (8.3)
Total	24 (100.0)

[1)]: Only one patient develops hepatitis.
PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; DTB, disseminated tuberculosis.

the first 35 and 55 days after the initiation of HAART. The overall prevalence of opportunistic and non-opportunistic intestinal parasites at HAART initiation was found to be 34.3%. The most common non-opportunistic intestinal parasites diagnosed in the study subjects were *Strongyloides stercoralis* 16 (14.8%), followed by *Ascaris lumbricoides* 9 (8.3%), *Entamoeba histolytica*/*dispar* 8 (7.5%) and *Giardia lamblia* 3 (2.8%). The only opportunistic intestinal parasite observed was *Isospora belli* from only one patient.

The mean ± SD CD4 and CD8 cells counts at the baseline for 185 patients were 123 ± 73 and 1,112 ± 887, respectively. Among the patients, 36.6% (56/162) and 28.4% (46/162) had elevated values for AST and ALT, with mean values of 40.3 and 36.4 U/l, respectively. Of 155 HIV/AIDS patients for whom baseline hemoglobin values were determined, 35.5% were anemic with hemoglobin concentrations of less than or equal to 11.5 gm%. The mean hemoglobin value of the patients was 12.3 gm%. According to the WHO standard, 13 (7.4%), 8 (4.6%), 26 (14.9%), 112 (64%), 13 (7.4%) and 3 (1.7%) patients were found to be severely malnourished, moderately malnourished, mildly malnourished, normal, overweight and obese, respectively.

According to WHO clinical staging criteria before the initiation of ART, a significant majority of the patients (67.2%) were classified under stage 3 followed by stage 4 (19.9%) and stage 2 (12.9%). Some of the patients (10.7%) were co-infected with syphilis. Patients with the above clinical stages were subjected to HAART. The predominant regimen provided was 1a (combinations of lamivudine, stavudine and nevirapine) (33.3%), followed by 1c (combination of combivir and nevirapine) (26.3%), 1d (combination combivir and efavirenz) (22.6%) and 1b (combination of lamivudine, stavudine and efavirenz) (17.7%).

The majority of the patients were followed for 6 months and their mean ± SD CD4 cell count increased significantly 6 months after treatment (212 ± 112, $P < 0.001$). About 30% (49/165) and 36.6% (60/164) of the patients had elevated AST and ALT values 6 months after initiation of HAART, respectively. This elevation was statically significant for AST ($P < 0.001$).

The proportion of patients with IRIS within the first 6 months of follow-up after initiation of HAART was found to be 17.2% (32/186). The mean days of IRIS occurrence for each disease ranged from 26 to 122 days with a mean (SD) of 80 (39) days (Figure 1).

As indicated in Table 2, compared to the baseline values the mean CD4 count, AST and ALT values increased significantly while the mean hemoglobin value decreased significantly for patients who developed IRIS ($P < 0.05$). And, the mean CD4 count and ALT values increased significantly while that of AST values decreased significantly among patients who did not develop IRIS. BMI, which is a proxy for nutritional assessment, was also determined, and a slight decrease in BMI was observed, from 18.6 to 18.4 before and after HAART initiation, respectively; however, the difference was not statistically significant ($P > 0.05$).

The type and frequencies of OIs after development of IRIS in the 32 patients are presented in Table 3. The most common infectious diseases associated with IRIS were TB and herpes zoster rash followed by cryptococcosis, toxoplasmosis and bacterial pneumonia. The prevalence of intestinal parasitosis at the time of IRIS development was 37.5% (9/24), in which *S. stercolaris*, *E. histolytica*/*dispar* and *G. lamblia* were observed in 4 (16.7%), 3 (12.5%) and 2 (8.3%) patients, respectively.

Twelve patients showed a clinical shift: eight patients from clinical stage 3 to 4, two patients from clinical stage 2 to 4, and one patient each from 2 to 3 and 3 to 2. Similarly, a treatment shift was made in 12 patients. A treatment shift from 1a to 1b and 1c to 1d was made for 4 and 3 patients, respectively. There was a shift from 1d to 1c, 1b to 1c, 1a to 1c, 1a to 1d and 1d to 1b for one patient each.

Out of the 32 patients who experienced IRIS, 3 died during the study period, 2 due to disseminated tuberculosis, and one due to cryptococcosis. Among the study subjects who did not develop IRIS, 5 died and 7 dropped out.

Logistic regression analysis using IRIS as dependent variable and sex, marital status, occupation, income, educational status, alcohol, qat chewing, smoking, hemoglobin, AST, ALT, CD4 count, nutritional status and religion as independent variables did not show any significant association with development of IRIS, except hemoglobin level, which showed a borderline significance ($P = 0.05$).

DISCUSSION

The proportion of IRIS among the 186 HIV/AIDS patients followed in the present study was 17.2%, and the mean days of IRIS occurrence after initiation of HAART ranged from 26 to 122 days with a mean of 80 days. These findings are in line with previous reports where 10 - 25% of patients who start HAART have experienced IRIS (5) and the time ranges between starting HAART and diagnosing IRIS have been from 8 to 416 days (5,8,12).

Immune reconstitution after initiation of HAART may be concurrent with both an increase in immunopathological responses against opportunistic pathogens and with the induction of IRIS. The IRIS phenomenon has been ascribed to various immune responses specific to underlying pathogens, with clinical manifestations related to the immune response elicited against such pathogens (4). And those individuals with IRIS have CD4 cell counts that have rapidly increased shortly after initiation of HAART. In our study too, 17.2% of patients experienced the events of IRIS within 6 months after HAART initiation. The majority of the events were due to TB (11.8%), out of which 5.4% were pulmonary TB, 4.3% were extrapulmonary TB, and 2.2% were disseminated TB. Similar reports from India and Thailand also showed 7.6 and 12.6% IRIS, respectively, and the cause was associated to *Mycobacterium tuberculosis* (13,14). However, the current proportion of TB was low compared with findings in Texas, where a higher rate (31.7%) of *M. tuberculosis* infection was reported (15). There were 4 cases that developed herpes zoster rash with mild and uncomplicated clinical manifestations in the present study. This is inconsistent with previous similar studies in which a 6 - 8% prevalence of zoster rash was observed (16).

Soon after the introduction of HAART, it was observed that some patients presented with initial or recurrent episodes of cryptococcal meningitis during the first weeks of therapy (17). In the current study, cryptococcal meningitis was observed in 3 (1.6%) individuals in the first weeks after HAART initiation. Similarly, 1 (0.5%) patient developed toxoplasmosis, 1 (0.5%) had toxoplasmosis and HBV co-infection and 1 (0.5%) developed bacterial pneumonia. Two patients developed hepatotoxicity with three- to fivefold increments in serum levels of AST and ALT. This finding is consistent with a study conducted by Becker (18), who reported elevated AST and ALT levels during HAART. This might be due to the direct effect of antiretroviral drugs, particularly nevirapine, which induces the development of hepatotoxicity (19). Two patients also developed severe anemia with hemoglobin values <6.9 gm%. This might be due to the nature of some antiretroviral drugs which have myelo-suppressive effect, especially with respect to the red blood cells, which eventually leads to the development of anemia (20). In line with this, our assessment of risk factors related to development of IRIS showed a borderline significant association to hemoglobin levels ($P = 0.05$).

HIV/AIDS also predisposes its victims to various opportunistic parasitic infections. Of these, *Cryptosporidum parvum*, *I. belli*, *Cyclospora cayetanensis* and *Microspordia* are the most frequent causes of diarrhea (21,22). In this study, the only opportunistic intestinal parasite observed was *I. belli* from only one patient (0.54%). This is a lower prevalence than those in similar studies carried out in Ivory Coast (3.9%) (22) and in Addis Ababa (3.4%) (23). The 34.5% prevalence of all intestinal parasitic infections was comparable to other previous studies in Ethiopia and elsewhere among HIV/AIDS patients (22,23).

In summary, the proportion of IRIS in Zewditu Memorial Hospital, Addis Ababa, Ethiopia was 17.2% out of 186 HAART-treated patients. The most prevalent opportunistic diseases were TB, herpes zoster rash and cryptococcosis. Low hemoglobin value was found to be a borderline risk factor for the development of IRIS. Based on the findings of this study, special training to increase awareness of IRIS would be of importance to clinicians and health care workers managing AIDS patients. In addition, the utmost effort should be made to increase the availability of laboratory facilities for the diagnosis of IRIS and also the provision of adequate antimicrobials and other medications for proper treatment of the patients. Further prospective surveys on epidemiological, immunological, microbial and clinical studies are also imperative to assess the proportion and pattern of IRIS and the effect of HAART in Ethiopia.

ACKNOWLEDGMENTS

The study was conducted with financial support of Addis Ababa University and University of Gondar.

The authors would like to thank the staffs of ART clinic, Zewditu Memorial Hospital and the staffs of regional laboratory, Addis Ababa for their technical support during data collection. It is also our pleasure to extend our gratitude for the willingness of the participants in the study.

REFERENCES

1. Robertson, J., Meier, M., Wall, J., et al. (2006): Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. J. Clin. Infect. Dis., 42, 1639-1646.
2. DeSimone, J.A., Pomerantz, R.J. and Babinchak, T.J. (2000): Inflammatory reactions in HIV-infected persons after initiation of highly active antiretroviral therapy. Ann. Intern. Med., 133, 447-454.
3. Hirsch, H.H., Kaufmann, G., Sendi, P., et al. (2004): Immune reconstitution in HIV-infected patients. Clin. Infect. Dis., 38, 1159-1166.
4. Pires, A., Nelson, M., Pozniak, A.-L., et al. (2005): Mycobacterial immune reconstitution inflammatory syndrome in HIV-1 infection after anti-retroviral therapy is associated with deregulated specific T-cell responses: beneficial effect of IL-2 and GM-CSF immunotherapy. J. Immun. Based Ther. Vac., 3, 2-11.
5. Ratnam, I., Chiu, C., Kandala, N.-B., et al. (2006): Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1-infected cohort. Clin. Infect. Dis., 42, 418-427.
6. Rubbert, A. and Ostrowski, M. (2005): Pathogenesis of HIV-1 infection. p. 59-63. *In* Kamps, H.R., HIV Medicine. 3rd ed. Flying Publisher, Paris.
7. Kottilil, S., Polis, M.-A. and Kovacs, J.A. (2004): HIV infection hepatitis

C infection and HAART: hard clinical choices. JAMA, 292, 243-250.
8. Puthanakit, T., Oberdorfer, P., Akarathum, N., et al. (2006): Immune reconstitution syndrome after highly active antiretroviral therapy in human immunodeficiency virus-infected Thai children. J. Pediatr. Infect. Dis., 25, 53-57.
9. World Health Organization (1995): Physical status: the use and interpretation of anthropometry. Report of WHO Expert Committee. World Health Organization Tech. Rep. Ser., 854, 1-452.
10. Cheesbrough, M. (1998): District laboratory practice in tropical countries. Part I. p. 191-239. Cambridge University Press, Cambridge, England.
11. World Health organization (2001): Iron Deficiency Anemia: Assessment, Prevention, and Control. World Health Organization.
12. Lawn, S., Bekker, R. and Miller, R. (2005): Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. Lancet Infect. Dis., 5, 361-370.
13. Kumarasamy, N., Chaguturu, S., Mayer, K.H., et al. (2004): Incidence of immune reconstitution syndrome in HIV/tuberculosis–coinfected patients after initiation of generic antiretroviral therapy in India. J. Acquired Immune Defic. Syndr., 37, 1574-1576.
14. Manosuthi, W., Kiertiburanakul, S., Phoorisri, T., et al. (2006): Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculosis and antiretroviral therapy. J. Infect. Dis., 11, 1-5.
15. Shelbure, S.-A., Visnegarwala, F., Darcourt, J., et al. (2005): Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. J. AIDS, 19, 339-404.
16. French, M.A., Price, P. and Stone, S.F. (2004): Immune restoration disease after antiretroviral therapy. AIDS, 18, 1615-1627.
17. Rambeloarisoa, J., Batisse, D., Thiebaut, J.-B., et al. (2002): Intramedullary abscess resulting from disseminated cryptococcosis despite immune restoration in a patient with AIDS. J. Infect., 44, 185-188.
18. Becker, S. (2004): Liver toxicity in epidemiological cohorts. Clin. Infect. Dis., 38, S49-55.
19. Wit, F.W.N.M., Weverling, G.J., Weel, J., et al. (2002): Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. J. Infect. Dis., 186, 23-31.
20. De Jesus, E., Herrera, G., Teofilo, E., et al. (2004): Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. Clin. Infect. Dis., 39, 1038-1046.
21. Smith, P.-D. and Lanc, H.-C. (1988): Intestinal infections in patients with the acquired immunodeficiency syndrome (AIDS). Ann. Intern. Med., 108, 328-333.
22. Therizol-Ferly, M., Tagliante-Saralino, J., Kone, M., et al. (1989): Chronic diarrhea and parasitosis in adult patients suspected to have AIDS in Ivory Coast. Bull. Soc. Pathol. Exot. Filiales, 92, 690-693.
23. Fisseha, B., Petros, B., Woldemichael, T., et al. (1999): Diarrhea associated parasitic infections agents in AIDS patients with selected Addis Ababa hospitals. Ethiop. J. Health Dev., 13, 169-171.