ORIGINAL ARTICLE

Lipodystrophy induced by combination antiretroviral therapy in HIV/AIDS patients: A Belgrade cohort study

Lipodistrofija indukovana kombinovanom antiretrovirusnom terapijom kod HIV/AIDS bolesnika

Gordana Dragović[*], Dragana Danilović[†], Aleksandra Dimić[†], Djordje Jevtović[‡]

[*]Institute of Pharmacology, Clinical Pharmacology and Toxicology, [‡]Institute of Infective and Tropical Diseases "Dr Kosta Todorovic", Faculty of Medicine, University of Belgrade, Belgrade, Serbia; [†]Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Abstract

Background/Aim. Highly active antiretroviral therapy (HAART) has led to dramatic reductions in mortality and morbidity of HIV/AIDS-patients. Lipodystrophy, a syndrome including peripheral fat wasting and central obesity, is well-documented side effect of HAART. The aim of this study was to evaluate the incidence of lipodystrophy, and to determine its risk ratios in a HIV/AIDS-cohort. **Methods.** This cross-sectional study included all the antiretroviral-naive HIV/AIDS patients commencing HAART from October 1, 2001 to October 1, 2010, at the HIV/AIDS Center, Institute of Infectious and Tropical Diseases, Belgrade, Serbia. Univariate and stepwise multivariate logistic regression analyses were used to determine the odds ratios (OR) with the confidence interval (CI) of 95%, in order to establish the relative risk for lipodystrophy. The Kaplan-Meier-method was used to determine the probability of development lipodystrophy over time. All statistical analyses were performed using SPSS software version using 0.05 as a p-treshold for the significance. **Results.** This study included 840 HIV/AIDS patients, 608 women and 232 men, followed for 5.6 ± 2.8 years. The prevalence of lipodystrophy was 69.2%. Univariate and stepwise multivariate regression analysis identified that the female gender, hepatitis C coinfection, AIDS diagnosis prior to HAART initiation, nucleoside-reverse-transcriptase-inhibitors and protease-inhibitors based regimens had a high risk for developing lipodystrophy in HIV/AIDS-patients (OR = 1.6, 95% CI = 1.1–3.49, $p = 0.04$; OR = 3.31, 95% CI = 1.3–6.8, $p < 0.01$; OR = 3.7, 95% CI = 1.7–6.1, $p < 0.01$; OR = 2.1, 95% CI = 1.7–3.3, $p < 0.01$; OR = 6.1, 95% CI = 4.1–9.7, $p < 0.01$, respectively). **Conclusion.** Despite much greater life expectancy of HIV/AIDS-patients, treatment-related toxicities still remain a major concern. Monitoring of lipodystrophy, as side effect of HAART, is particularly important.

Key words:
lipodistrophy; incidence; risk factors; hiv; antiretroviral therapy, highly active; sex; hepatitis c.

Apstrakt

Uvod/Cilj. Visokoaktivna antiretrovirusna terapija (HAART) dovela je do značajnog sniženja mortaliteta i morbiditeta kod bolesnika sa HIV/AIDS-om. Lipodistrofija, sindrom definisan perifernim gubitkom masnog tkiva, praćen istovremenom centralnom gojaznošću, predstavlja dokumentovani neželjeni efekat HAART–a. Cilj ovog istraživanja bio je da se utvrdi incidencija lipodistrofije i da se determinišu potencijalni faktori rizika od njenog nastanka i razvoja kod pacijenata sa HIV/AIDS-om koji su lečeni HAART-om. **Metode.** Retrospektivnom studijom bili su obuhvaćeni svi HIV/AIDS pacijenti koji nikada ranije nisu bili lečeni HAART-om i koji su započinjali naznačenu terapiju u periodu od 01.10.2001. do 01.10.2010. u Centru za HIV/AIDS Instituta za infektivne i tropske bolesti, Beograd, Srbija. Univarijantna i naknadna multivarijanta logistička regresiona analiza primenjene su da bi se utvrdio odnos šansi (OR) i interval poverenja od 95% (95% CI) u cilju procene relativnog rizika od razvoja lipodistrofije. Kaplan-Majerova analiza korišćena je u cilju procene verovatnoće razvoja lipodistrofije tokom vremena. Sve korišćene statističke analize rađene su primenom SPSS softverskog paketa, pri čemu je $p < 0.05$ smatrano statistički značajno. **Rezultati.** U studiju je bilo uključeno ukupno 840 HIV/AIDS-pacijenata, 608 muškog i 232 ženskog pola, koji su praćeni 5.6 ± 2.8 godina. Prevalencija lipodistrofije iznosila je 69.2%. Univarijantna i naknadna multivarijantna regresiona analiza identifikovale su ženski pol (OR = 1.6; 95% CI = 1.1–3.49, $p = 0.04$), istovremenu infekciju he-

Correspondence to: Gordana Dragović, Institute of Pharmacology, Clinical Pharmacology and Toxicology, Faculty of Medicine, University of Belgrade, Dr Subotića 1/III; 11 000 Belgrade, Serbia. Phone: 065 27 21 180. E-mail: gozza@beotel.net

patitis C virusom (OR = 3,31, 95% CI =1,3–6,8, $p < 0,01$), AIDS pre započinjanja HAART-a (OR = 3,7; 95% CI = 1,7–6,1, $p < 0,01$), nukleozidne inhibitore reverzne transkriptaze (OR = 2,1, 95% CI = 1,7–3,3, $p < 0,01$) i proteazne inhibitore (OR = 6,1, 95% CI = 4,1 – 9,7, $p < 0,01$), kao nezavisne prediktore za razvoj lipodistrofije kod pacijenata inficiranih HIV-om. **Zaključak.** Uprkos značajnom produženju života pacijenata sa HIV/AIDS-om, toksičnost indukovana primenom HAART-a i dalje predstavlja značajan problem. Upravo zato, praćenje pojave i razvoja lipodistrofije, kao neželjenog efekta HAART-a, jeste od izuzetne važnosti.

Ključne reči:
lipodistrofija; incidenca; faktori rizika; hiv; lečenje antiretroviroticima, visokoaktivno; pol; hepatitis c.

Introduction

The use of highly active antiretroviral therapy (HAART), in treatment of human immunodeficiency virus (HIV) has led to dramatic reductions in mortality and morbidity of patients [1]. From a very bad prognosis in its beginnings, HIV infection and acquired immunodeficiency syndrome (AIDS) meanwhile became the chronic disease, which can be treated, controlled and supervised.

HAART usually consists of the combination of two drugs from the nucleoside reverse transcriptase inhibitors (NRTI) group, and a single drug from the protease inhibitors (PI) group (2 NRTIs + 1 PI) or of one non-nucleoside reverse transcriptase inhibitor (NNRTI). The latter combination (2 NRTIs + 1 NNRTI) is equally efficient as the first one, so that the PIs are often reserved for the later stages of the treatment due to their higher resistance barrier [2].

Lipodystrophy, a syndrome including peripheral fat wasting and central obesity, which in some patients may be followed with metabolic changes such as hyperlipidemia and glucose intolerance, or diabetes mellitus, is well-documented side effect of HAART [3, 4]. Changes in body composition include lipoatrophy, a complete or partial loss of adipose tissue predominantly in limbs and face and lipohypertrophy, which is pathological accumulation of adipose tissue in the omentum, mesenterium, retroperitoneum and pelvis, dorso-cervical region, or breast enlargement in women [5]. Lipoatrophy and lipohypertrophy may or may not coexist. Reported prevalence rates of lipodystrophy range from a few percent to over 80% [4, 5].

The aim of this study was to evaluate the incidence of lipodystrophy, and to determine the relative risk rates of this side effect of HAART, in HIV/AIDS cohort of antiretroviral-naive patients commencing HAART in Belgrade, Serbia.

Methods

This cross-sectional study included all eligible HIV-infected patients receiving HAART at the HIV/AIDS Center of Institute of Infectious and Tropical Diseases, Clinical Center of the Republic of Serbia, Belgrade.

To be eligible in the study, a patient had to be 18 or older, with documented HIV infection [6], antiretroviral-naive patients commencing HAART from October 1, 2001 to October 1, 2010, and with collected data about the occurrence of lipodystrophy. The clinical diagnosis of lipo-dystrophy was made on the basis of physical examination, by recognizing changes such as fat loss from face, arms and legs, and accumulation of fat in the abdominal and/or dorso-cervical region, including breast enlargement in women, as described in the European AIDS Clinical Society (EACS) guidelines [7].

The exclusion criteria were: simultaneous therapy with corticosteroids, anabolic steroids, as well as the treatment of some of the AIDS-related opportunistic infections, within 3 months before the lipodystrophy diagnosis.

During the study period, 25 antiretroviral drugs were registered worldwide, of which the following were also registered in Serbia: zidovudine, didanosine, lamivudine, stavudine, zalcitabine and abacavir (from the NRTI group), nevirapine and efavirenz (from the NNRTI group), saquinavir, nelfinavir, indinavir, fosamprenavir, lopinavir/ritonavir, and ritonavir for boosting other PIs (from the PI group). Nelfinavir and indinavir were withdrawn in 2008. Enfuvirtide was introduced in 2007 for salvage regimens. Newer drugs, such as tenofovir/emtricitabine, tipranavir, atazanavir, etravirine, raltegravir, as well as maraviroc, were not included among the drugs reimbursed by the national health insurance system during the study period.

The immunological and virological responses to HAART were evaluated every 4–6 months by measuring plasma viral loads (pVL) and CD4+ T-cell counts. Due to shortages, HAART monitoring was not performed regularly, which led to the delay in the measurements of CD4+ T-cell counts and viral loads. CD4 cells were quantified by flow-cytometry. Plasma HIV-1 RNA loads were measured by quantitative reverse transcriptase polymerase chain reaction (ultrasensitive assay version 1.5, Roche Molecular Systems, Branchburg, NJ, USA), with a lower limit of detection of 50 copies/mL ($1.7 \log_{10}$).

All statistical analyses were performed using SPSS software version using 0.05 as a p treshold for the significance. Possible associations between lipodystrophy and gender, age above 40, coinfection with hepatitis C virus, AIDS [7] at HAART initiation and the type of HAART regimen, were tested. Univariate and stepwise multivariate logistic regression analyses were used to determine the odds ratios (OR), with the confidence interval (CI) of 95%, in order to establish the relative risk for the occurrence of lipodystrophy. The Kaplan-Meier product limit method were used to determine the probability of developing lipodystrophy over time.

The study was approved by the Clinical Center of Serbia Ethics Committee, Belgrade, Serbia.

Results

This study included 840 HIV/AIDS patients, followed for a mean period of 5.6 ± 2.8 years. There were 608 (72.4%) men and 232 (27.6%) women. The median age was 43.5 years (range: 22–58 years). Along with HIV, 216 (25.7%) patients were coinfected with hepatitis C virus (HCV), and 52 (6.2%) patients with hepatitis B virus (HBV). The median CD4+ cell count was 347 cells/mm^3 (range: 183–455 cells/mm^3).

HAART regimens included the following: combinations of two NRTIs as a treatment backbone, with one or two PIs (taken by 14.3% of all the patients), or one NNRTI (33.3%), and multiple combinations of drugs from all the classes (52.4%).

The prevalence of lipodystrophy was 69.2%. The overall estimated probability of developing lipodystrophy increased with time, reaching 100% after ten years of treatment, with median time of 7 years for the development of lipodystrophy in 50% of patients (Figure 1). In the subgroup of patients coinfected with HCV, the prevalence of lipodystrophy was 41%, as opposed to 25.8% among those without HCV (p < 0.01).
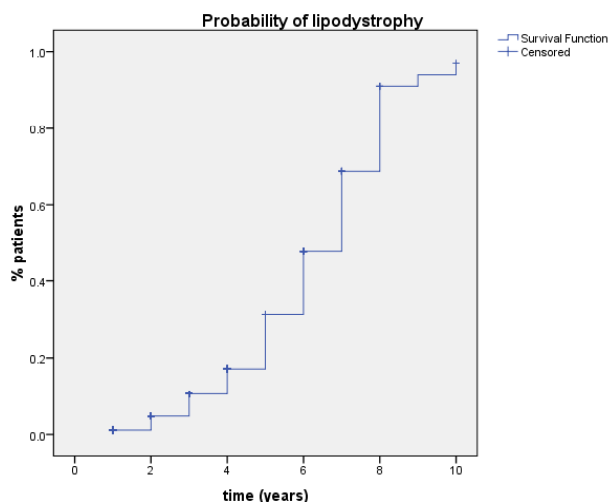

Fig. 1 – The estimated probability (Kaplan-Meier product limit method) of developing lipodistrophy over time.

Univariate logistic regression analysis (Table 1) showed that female gender, age above 40, HCV coinfection, AIDS at HAART initiation, and prolonged usage of NRTIs, were all associated with lipodystrophy. Among the NRTIs, multivariate logistic regression analysis indicated that highest risk for lipodystrophy was associated with the usage of stavudine, didanosine and zidovudine. In contrast with this, lamivudine and abacavir were not significant predictors (OR 2.1, 95% CI 1.6–3.9, p = 0.09; OR 3.3, 95% CI 1.7–4.1, p = 0.6, respectively). The usage of NNRTI based regimens carried a lower risk for lipodystrophy (OR 2.1, 95% CI 1.2–3.3, p < 0.01). The same analysis showed that the PI regimens were also associated with the development of lipodystrophy (OR 5.9, 95% CI 3.7–9.6, p < 0.001). The stepwise multivariate regression analysis identified that the PI based regimens had together with NRTI drugs, female gender, HCV coinfection, and AIDS diagnosis prior to HAART initiation, a high risk for developing lipodystrophy in HIV/AIDS patients (Table 1).

Discussion

Within the recognition that HIV production could be suppressed, but not eradicated, the focus of antiretroviral therapy in the mid-1990s was to convert the infection from uniformly fatal disease into a long term, manageable condition. This accomplishment was reported in 1998, with the seminal publication from the Multicenter AIDS Cohort Study (MACS), associating a dramatic drop in death rates from AIDS with the widespread application of HAART in the USA [1]. However, as patients may potentially be exposed to HAART for decades, treatment-associated toxicities, such as lipodystrophy, remains a concern.

The frequency of lipodystrophy in the Belgrade cohort was 69.2%, which was in correlation with the results of Miller et al. [8]. Some previous studies had shown a lower prevalence of lipodystrophy, but that was probably in connection with the lack of precise definition of the syndrome, and the fact that only the most severe cases had been registered [9–11].

We also showed that the probability of developing lipodystrophy increases with time, reaching 100% by 10 years of HAART and with the median time of 7 years for the development of lipodystrophy. Lipodystrophy identification had

Table 1

Risk factors for lipodystrophy

Variable	Univariate analysis			Multivariate analysis		
	OR	(95% CI)	p	OR	(95% CI)	p
Female gender	1.6	(2.12–4.8)	< 0.01	1.6	(1.1–3.49)	0.04
Age above 40 (years)	1.9	(1.4–3.8)	0.01	–		–
HCV coinfection	2.4	(1.8–4.3)	0.01	3.31	(1.3–6.8)	< 0.01
AIDS at HAART initiation	1.6	(1.1–3.9)	0.02	3.7	(1.7–6.1)	< 0.01
NRTIs (prolonged usage)	2.9	(1.4–5.1)	< 0.01	2.1	(1.7–3.3)	< 0.01
d4T	6.7	(1.8–8)	< 0.01	4.8	(1.61–5.59)	< 0.01
ddI	4.6	(2.2–6.8)	< 0.01	4.2	(2.82–5.71)	< 0.01
AZT	2.2	(1.2–3.9)	0.02	2.1	(1.51–3.86)	< 0.01
PIs	5.9	(3.7–9.6)	< 0.01	6.1	(4.1–9.7)	< 0.01

HCV – hepatitis C virus; AIDS – acquired immunodeficiency syndrome; HAART – highly active antiretroviral therapy; NRTI – nucleoside reverse transcriptase inhibitors; d4T – stavudine; ddI – didanosine; AZT – zidovudine; PIs – protease inhibitors; OR – odds ratio; CI – confidence iterval.

profound implications for the management of HIV/AIDS. Its recognition as a side effect of HAART led to the reevaluation of the appropriate time to start the therapy and also to various modifications in therapy of HIV.

Numerous cross-sectional studies and many prospective cohort studies analyzed the occurrence of lipodystrophy, and attempted to determine the factors that cause it. In our study, both the age above 40 and AIDS diagnosis at HAART initiation were associated with lipodystrophy, but the age above 40 was not an independent predictor. Several studies have demonstrated that the older age and AIDS diagnosis prior to HAART initiation are the risk factors for lipodystrophy [12–14]. There are conflicting data regarding the risks associated with gender. Martinez et al. [15], in their study, found that the female gender is in higher risk for lipodystrophy. Thiebaut et al. [16], on the other hand, came to the contrary conclusions, that the female gender was not in higher risk for lidodistrophy. Several other studies established HCV coinfection as an independent predictor of lipodistrophy, demonstrating the association of HCV co-infection with higher rates of lipodystrophy [17–19].

NRTIs, especially thymidine analogues, are known to cause mitochondrial toxicity [20]. Given the similarities in function between HIV reverse transcriptase and human DNA polymerase, it is not surprising that nucleoside analogues are competitive inhibitors of human DNA polymerase-gamma, a key enzyme for mitochondrial DNA (mtDNA) replication. The accumulation of mtDNA deficits induces a deficient production of molecules devoted to the intramitochondrial synthesis of adenosine triphosphate (ATP). Once ATP production drops below a certain threshold, sudden mitochondrial and then cellular damage occurs that can lead to cell death. Tissues and organs cannot function properly, and the damage becomes clinically apparent [21]. The clinical use of NRTI has been associated with adverse effects caused by mitochondrial dysfunction, such as acute pancreatitis, myopathy, peripheral neuropathy, anemia, neutropenia, hepatic toxicity and hyperlactataemia/lactic acidosis [20–22]. Our data show that the prolonged usage of NRTIs, especially thymidine analogues such as stavudine, didanosine and zidovudine, is likely to be associated with the development of lipodystrophy, which is in accordance with numerous other studies [23–25]. NRTIs induce lipodystrophy by way of mitochondrial toxicity, which is not the case with PIs and NNRTIs. Moreover, NNRTI based HAART is less likely to induce lipodystrophy than the PI based HAART [26].

Lipodystrophy syndrome, together with the insulin resistance, type 2 diabetes mellitus and hyperlipidemia develop a cluster of metabolic abnormalities, referred to as the metabolic syndrome. Metabolic syndrome, increases the cardiovascular risk and has great impact on life expectancy in HIV/AIDS patients [27].

Life style modifications and exercise training, antiretroviral switch strategies, pharmacological management (rosiglitazone, metformin, human growth hormone, human growth hormone–releasing factor, leptin, etc) and reconstructive surgery could be possible treatment options for lipodystrophy syndrome [14].

The initial enthusiasm of clinicians with HAART success, primarily because of the possibility of the long-term control of HIV replication, is suppressed with the new knowledge about the potential toxicity of antiretroviral drugs. For some patients lipodystrophy is only a cosmetic problem, but for others the very same problem may affect their future decisions on the treatment, making them cease the therapy or significantly reduce treatment compliance. As the result, the patients may experience rebound in viral load or the development of viral resistance. This would eventually lead to disease progression and even to an increased risk of disease transmission, possibly by a drug resistant viral strain [28].

Conclusion

Despite much greater life expectancy of HIV/AIDS patients, treatment related toxicities still remain a major concern. Monitoring of the side effects of highly active antiretroviral therapy, such as lipodystrophy is, particularly important.

Acknowledgments

R E F E R E N C E S

1. *Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT*, et al. HIV Outpatient Study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. J Acquir Immune Defic Syndr 2006; 43(1): 27−34.

2. *Clumeck N, Pozniak A, Raffi F*. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults. HIV Med 2008; 9(2): 65−71.

3. *Garg A*. Acquired and inherited lipodystrophies. N Engl J Med 2004; 350(12): 1220−34.

4. *Safrin S, Grunfeld C*. Fat distribution and metabolic changes in patients with HIV infection. AIDS 1999; 13(18): 2493−505.

5. *Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ*, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 1998; 12(7): 51−8.

6. CDC. Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992; 41(RR−17): 1−19.

7. *Lundgren JD, Battegay M, Behrens G, De WS, Guaraldi G, Katlama C*, et al. European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. HIV Med 2008; 9(2): 72−81.

8. *Miller J, Carr A, Emery S, Law M, Mallal S, Baker D*, et al. . HIV lipodystrophy. Prevalence, severity and correlates of risk in Australia. HIV Med 2003; 4(3): 293−301.

9. *Freitas P, Carvalho D, Santos AC, Madureira AJ, Xerinda S, Martinez E*, et al. Central/Peripheral fat mass ratio is associated

with increased risk of hypertension in HIV-infected patients. J Clin Hypertens (Greenwich) 2012; 14(9): 593−600.

10. *Freitas P, Carvalho D, Santos AC, Mesquita J, Matos MJ, Madureira AJ*, et al. Lipodystrophy defined by Fat Mass Ratio in HIV-infected patients is associated with a high prevalence of glucose disturbances and insulin resistance. BMC Infect Dis 2012; 12: 180.

11. *Piloya T, Bakeera-Kitaka S, Kekitiinwa A, Kamya MR.* Lipodystrophy among HIV-infected children and adolescents on highly active antiretroviral therapy in Uganda: a cross sectional study. J Int AIDS Soc 2012; 15(2): 17427.

12. *Luetkemeyer AF, Havlir DV, Currier JS.* Complications of HIV disease and antiretroviral therapy. Top Antivir Med 2012; 20(2): 48−60.

13. *Domingo P, Estrada V, López-Aldeguer J, Villaroya F, Martínez E.* Fat redistribution syndromes associated with HIV-1 infection and combination antiretroviral therapy. AIDS Rev 2012; 14(2): 112−23.

14. *Singhania R, Kotler DP.* Lipodystrophy in HIV patients: its challenges and management approaches. HIV AIDS (Auckl) 2011; 3: 135−43.

15. *Martinez E, Mocroft A, García-Viejo MA, Pérez-Cuevas JB, Blanco JL, Mallolas J,* et al. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. Lancet 2001; 357(9256): 592−8.

16. *Thiebaut R, Daucourt V, Mercie P, Ekouevi DK, Malvy D, Morlat P,* et al. Lipodystrophy, metabolic disorders, and human immunodeficiency virus infection: Aquitaine Cohort, France, 1999. Clin Infect Dis 2000; 31(6): 1482−7.

17. *Loko MA, Bani-Sadr F, Winnock M, Lacombe K, Carrieri P, Neau D,* et al. Impact of HAART exposure and associated lipodystrophy on advanced liver fibrosis in HIV/HCV-coinfected patients. J Viral Hepat 2011; 18(7): e 307−14.

18. *Laguno M, Milinkovic A, Lazzari E, Murillas J, Martínez E, Blanco JL,* et al. Incidence and risk factors for mitochondrial toxicity in treated HIV/HCV-coinfected patients. Antivir Ther 2005; 10(3): 423−9.

19. *Sulkowski MS, Benhamou Y.* Therapeutic issues in HIV/HCV-coinfected patients. J Viral Hepat 2007; 14(6): 371−86.

20. *McComsey G, Bai R, Maa J, Seekins D, Wong L.* Extensive investigations of mitochondrial DNA genome in treated HIV-infected subjects: beyond mitochondrial DNA depletion. J Acquir Immune Defic Syndr 2005; 39(2): 181−8.

21. *Koczor CA, Lewis W.* Nucleoside reverse transcriptase inhibitor toxicity and mitochondrial DNA. Expert Opin Drug Metab Toxicol 2010; 6(12): 1493−504.

22. *Dragović GJ, Smith CJ, Jevtović DL, Johnson MA, Ranin J, Salemović D,* et al. Comparison of nucleoside reverse transcriptase inhibitor use as part of first-line therapy in a Serbian and a UK HIV clinic. HIV Clin Trials 2009; 10(5): 306−13.

23. *van Oosterhout JJ, Mallewa J, Kaunda S, Chagoma N, Njalale Y, Kampira E,* et al. Stavudine toxicity in adult longer-term ART patients in Blantyre, Malawi. PLoS One 2012; 7(7): e42029.

24. *Domingo P, Cabeza MC, Pruvost A, Salazar J, Gutierrez MD, Mateo MG,* et al. Relationship between HIV/Highly active antiretroviral therapy (HAART)-associated lipodystrophy syndrome and stavudine-triphosphate intracellular levels in patients with stavudine-based antiretroviral regimens. Clin Infect Dis 2010; 50(7): 1033−40.

25. *Bussmann H, Wester WC, Thomas A, Novitsky V, Okezie R, Muzenda T,* et al. Response to zidovudine/didanosine-containing combination antiretroviral therapy among HIV-1 subtype C-infected adults in Botswana: two-year outcomes from a randomized clinical trial. J Acquir Immune Defic Syndr 2009; 51(1): 37−46.

26. *Lugassy DM, Farmer BM, Nelson LS.* Metabolic and hepatobiliary side effects of antiretroviral therapy (ART). Emerg Med Clin North Am 2010; 28(2): 409−19.

27. *Potthoff A, Brockmeyer NH, Gelbrich G, Neuhaus K, Esser S, Reinsch N,* et al. Lipodystrophy - a sign for metabolic syndrome in patients of the HIV-HEART study. J Dtsch Dermatol Ges 2010; 8(2): 92−8.

28. *Ammassari A, Murri R, Pezzotti P, Trotta MP, Ravasio L, de Longis P,* et al. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. J Acquir Immune Defic Syndr 2001; 28(5): 445−9.