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Original Article

Correlation between cardiovascular risk factors in HIV-infected patients and three highly active anti-retroviral therapy regimens

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Abstract: Objective: To analyze the correlation between three highly active anti-retroviral therapy (HAART) regimens and cardiovascular risk factors in patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS). Methods: One hundred and eight patients with HIV/AIDS were randomly divided into three groups. Different HAART regimens were given to each of the groups. Group A: lamivudine + zidovudine + nevirapine; Group B: lamivudine + tenofovir + efavirenz; Group C: lamivudine + tenofovir + lopinavi/ritonavir (LPV/r). $CD4^+$T lymphocyte count, body mass index (BMI), ankle-brachial index (ABI), blood pressure, blood sugar, blood lipid and carotid ultrasound were measured before treatment and after 12 months of treatment. Immune reconstitution was assessed after treatment, and changes of cardiovascular risk factors in the three groups were compared. Results: The $CD4^+$T lymphocyte count in the three groups after 6, 12, and 24 months of treatment was significantly higher than that before treatment ($P<0.05$), while the count showed no significant difference among the three groups at each time point ($P>0.05$). After 24 months of treatment, the cardiovascular risk factors showed significant changes in the three groups ($P<0.05$), and there were significant differences in the systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), intima-media thickness (IMT) between Group C and Groups A and B ($P<0.05$); the cardiovascular risk stratification in Group C was more severe than that in Groups A and B ($P<0.05$); the incidence of hyperglycemia and hypercholesterolemia in Group C was significantly higher than that in Groups A and B ($P<0.05$). Conclusion: The three HAART regimens have similar effects on immune reconstitution and can lead to increased cardiovascular risk of patients, with the lamivudine + tenofovir + LPV/r group at greatest risk, which needs attention to in clinical work.

Keywords: AIDS, HAART, immune reconstitution, cardiovascular risk

Introduction

AIDS, namely acquired immunodeficiency syndrome, is a serious infectious disease caused by human immunodeficiency virus (HIV) infection [1]. HIV mainly damages the immune system dominated by $CD4^+$T lymphocytes, leading to the decline of the defense ability of the body. Therefore, AIDS patients are highly susceptible to opportunistic infections and tumors that are less common in healthy individuals, ultimately resulting in death [2]. As a malignant infectious disease with rapid spread and high mortality, AIDS hinders economic development and seriously endangers human health. Moreover, it has become a public health and social issue due to its widespread presence in the world. Currently, the recommended antiviral therapy for HIV/AIDS is the "cocktail therapy" invented by Professor David Ho, internationally called high active anti-retroviral therapy (HARRT) [3]. It minimizes viral load, protects and rebuilds part of the immune functions, as well as reduces the incidence of opportunistic infections [4]. Although the popularization of HAART has decreased fatalities, prolonged survival and reduced the incidence of opportunistic infections and tumors in HIV/AIDS patients, the mortality caused by related complications such as cardiovascular disease (CVD) has increased year by year [5]. Anti-retroviral (ARV) drugs can effectively inhibit the virus, however,

they may also lead to hyperlipidemia, fat redistribution, elevated blood sugar and insulin resistance, collectively known as lipodystrophy syndrome [6]. At present, some ARV drugs, such as stavudine, zidovudine, efavirenz, and protease inhibitors, have been reported to be highly correlated with fat metabolism [7]. Efavirenz may be related to hypercholesterolemia, while nevirapine is not. Dyslipidemia caused by stavudine-based antiviral therapy is characterized by the early presence of significantly elevated triglycerides and cholesterol [8]. Lipodystrophy is one of the major cardiovascular risk factors that manifests as increased risk of CVD and metabolic diseases, increased predictive factors for acute myocardial infarction, and development of subclinical arteriosclerosis.

Domestic and foreign studies mainly focus on the effects of HAART drugs, limited to individual drug classes or individual drugs, on dyslipidemia and metabolism [9]. In this study, the correlation among the three HAART regimens and cardiovascular risk factors in HIV/AIDS was discussed. Assuming that all of three regimens can increase the risk of cardiovascular disease, the regimen of lamivudine + tenofovir + lopinavir/ritonavir led to the highest increase, which is worthy of clinical attention.

Materials and methods

Clinical data

A total of 108 HIV/AIDS patients admitted to Sichuan Mianyang 404 Hospital from January 2016 to January 2017 were selected and randomly divided into Group A (35 cases), Group B (40 cases) and Group C (33 cases). Patients voluntarily signed informed consent forms and were willing to be followed throughout the study. This study was approved by the Ethics Committee of Sichuan Mianyang 404 Hospital.

Drugs and treatments

Three groups of patients were treated with three different HAART regimens. Group A: lamivudine + zidovudine + nevirapine; Group B: lamivudine + tenofovir + efavirenz; Group C: lamivudine + tenofovir + lopinavir/ritonavir (LPV/r). Lamivudine (Fujian Cosunter Pharmaceutical Co., Ltd.): 100 mg/qd, taken orally before breakfast. Zidovudine (Zhejiang Hisun Pharmaceutical Co., Ltd.): 600 mg/bid. Nevirapine (Kunshan Rotam Reddy Pharmaceutical Co., Ltd.): 200 mg/qd, changed to 200 mg/bid after 2 weeks. Tenofovir (tenofovir dipivoxil fumarate tablets, Anhui Biochem Pharmaceutical Co., Ltd.): 300 mg/qd. Efavirenz (Zhejiang Huahai Pharmaceutical Co., Ltd.): 600 mg/qd, taken before sleep. LPV/r (AbbVie Deutschland GmbH&Co.KG): 800 mg/bid. The treatment lasted for 2 years.

Inclusion and exclusion criteria

Inclusion criteria: (1) All patients meeting the diagnostic criteria for HIV infection in Diagnosis and Treatment of Aids Onset [10], HIV-1 positive tested by ELISA and confirmed by western blot; (2) Patients aged 30-70 years old; (3) Patients receiving no HIV antiviral therapies before grouping.

Exclusion criteria: (1) Patients complicated with hypertension, heart disease, diabetes, chronic renal insufficiency or other metabolic diseases; (2) Menopausal women; (3) Pregnant or lactating women; (4) Patients with severe mental diseases; (5) Patients with poor treatment compliance; (6) Patients combined with severe organ dysfunctions, severe infections or tumors; (7) Patients intolerant or allergic to the drugs used in the study; (8) Patients that were followed up for less than 24 months.

Clinic parameters

(1) The changes of T lymphocyte subsets in the peripheral blood were detected by flow cytometry (BD Company, USA, FACSCalibur) before treatment and after 6, 12, and 24 months of treatment, respectively. (2) The body mass and height of the patients were measured before treatment and after 24 months of treatment to calculate the body mass index (BMI). The diastolic blood pressure (DBP) and systolic blood pressure (SBP) were determined. Peripheral venous blood was drawn after 8 hours of fasting, then fasting plasma glucose (FPG), triacyl glycerol (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) were detected. (3) The intima-media thickness (IMT) were detected by ultrasonic diagnostic techniques and ankle-brachial index (ABI) of the patients were measured before treatment and after 24 months of treatment respectively. (4) After 24 months of treatment, Faminghan risk

Table 1. Comparison of baseline data of three groups of patients ($\bar{x} \pm sd$)

Baseline data	Group A (n=35)	Group B (n=40)	Group C (n=33)	F/χ^2	P
Gender (n)				0.184	0.912
Male	21	25	19		
Female	14	15	14		
Average age (year)	46.20±6.30	47.80±8.10	45.60±6.00	0.991	0.375
BMI (kg/m^2)	23.12±2.18	23.07±1.65	22.86±2.25	0.158	0.854
SBP (mmHg)	116.38±15.23	114.38±14.37	117.03±16.20	0.294	0.746
DBP (mmHg)	75.86±18.39	73.21±16.48	75.49±16.99	0.262	0.770
FPG (mmol/L)	5.13±0.72	5.24±0.87	5.02±0.69	0.739	0.480
TG (mmol/L)	1.59±0.54	1.63±0.59	1.54±0.33	0.285	0.753
TC (mmol/L)	3.97±0.75	4.06±0.80	4.01±0.75	0.129	0.879
HDL-C (mmol/L)	1.37±0.30	1.32±0.36	1.39±0.32	0.445	0.642
IMT (mm)	0.83±0.34	0.85±0.21	0.81±0.26	0.195	0.823
ABI	1.21±0.22	1.17±0.18	1.27±0.24	2.005	0.140
Smoking history (n)				0.986	0.611
Yes	29	34	30		
No	6	6	3		

Note: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triacyl glycerol; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; IMT, intima-media thickness; ABI, ankle-brachial index.

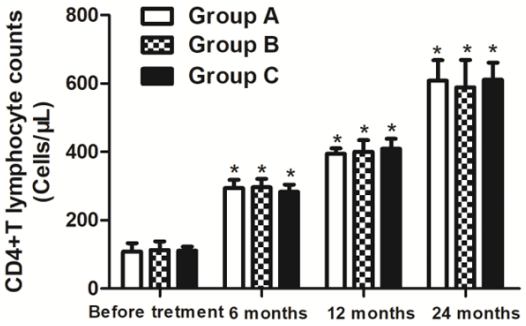

Figure 1. Changes of CD4$^+$T lymphocyte count before and after treatment. Compared with before treatment, *P<0.05.

score (FRS) was calculated according to the patient's age, sex, TC, HDL-C, SBP and smoking history, so as to predict the possibility of cardiac adverse events in the next 10 years. The patients were divided into low risk (<10%), moderate risk (10-20%) and high risk (>20%) [11]. The cardiovascular risk stratification in the three groups was compared. (5) After 24 months of treatment, the incidence of cardiovascular related diseases among the three groups was compared. Pa-tients with BMI ≥24.0 were considered overweight; SBP ≥140 mmHg and/or DBP ≥90 mmHg or taking antihypertensive drugs in the past two weeks considered as hypertension; FPG ≥6.10 mmol/L as hyperglycemia; FPG ≥7.0 mmol/L as diabetes; TG ≥1.70 mmol/L as hypertriglyceridemia; TC ≥5.70 mmol/L as hypercholesterolemia [10].

Statistical analysis

SPSS 22.0 was used for data processing and analysis. The measurement data were expressed as mean ± SD. One-way analysis of variance (ANOVA) was used for comparison among the three groups. Bonferroni method was adopted for the following pairwise comparison. The counting data were expressed as (n/%). The comparison among the three groups was conducted by χ^2 test, and the pairwise comparison was carried out afterwards. The comparison of cardiovascular risk stratification among the three groups was carried out by Kruskal-Wallis H test and pairwise comparison was performed. The difference was statistically significant with P<0.05.

Results

Comparison of baseline data

There was no significant difference in sex, mean age, BMI and SBP, DBP, FPG, TG, TC, HDL-C, IMT, ABI and smoking history among the three groups before treatment (P>0.05), as shown in **Table 1**.

Table 2. Comparison of cardiovascular risk factors after 24 months of treatment ($\bar{x}$ ± sd)

Risk factors	Group A (n=35)	Group B (n=40)	Group C (n=33)	F	P
BMI (kg/m^2)	24.27±2.94	24.18±2.10$^{\&}$	24.97±2.41$^{\&}$	1.045	0.355
SBP (mmHg)	126.37±10.26$^{\&}$	125.27±9.74$^{\&}$	133.64±8.31$^{*,\#,\&}$	7.979	0.001
DBP (mmHg)	81.36±6.37$^{\&}$	80.84±7.21$^{\&}$	84.74±6.49$^{*,\#,\&}$	8.154	0.001
FPG (mmol/L)	5.64±0.81$^{\&}$	5.70±0.93	5.73±0.78$^{\&}$	0.097	0.908
TG (mmol/L)	1.54±0.64	1.51±0.53	1.69±0.44$^{\&}$	1.095	0.338
TC (mmol/L)	5.12±0.89$^{\&}$	5.06±0.78$^{\&}$	5.67±0.81$^{*,\#,\&}$	5.737	0.004
HDL-C (mmol/L)	1.21±0.27$^{\&}$	1.19±0.20	1.15±0.35$^{\&}$	0.417	0.660
IMT (mm)	1.04±0.33$^{\&}$	0.97±0.28$^{\&}$	1.16±0.21$^{*,\#,\&}$	10.34	<0.001
ABI	1.19±0.20	1.11±0.26	1.24±0.30$^{*,\#}$	2.415	0.094

Note: compared with group A, *P<0.05; compared with group B, $^{\#}$P<0.05; compared with the group before treatment, $^{\&}$P<0.05. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; TG, triacyl glycerol; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; IMT, intima-media thickness; ABI, ankle-brachial index.

Table 3. Comparison of cardiovascular risk stratification after 24 months of treatment

Group	Case number	Low-risk	Middle-risk	High-risk
Group A	35	21	10	4
Group B	40	24	11	5
Group C	33	12	12	9

Changes of CD4$^+$T lymphocyte count

The CD4$^+$T lymphocyte count in the three groups after 6, 12, and 24 months of treatment was significantly higher than that before treatment (P<0.05), while the count showed no significant difference between the three groups at each time point (P>0.05). As shown in **Figure 1**.

Changes of cardiovascular risk factors

Before treatment, there was no significant difference in cardiovascular related risk factors (BMI, SBP, DBP, FPG, TG, TC, HDL-C, IMT, and ABI) among the three groups (all P>0.05, **Table 1**). After 24 months of treatment, there were significant differences in SBP, DBP, TC, and IMT between group C and groups A and B. Moreover, SBP, DBP, FPG, TC, HDL-C, IMT in group A showed significant changes (all P<0.05), as well as BMI, SBP, DBP, TC, IMT in group B (all P<0.05), and BMI, SBP, DBP, FPG, TG, TC, HDL-C, IMT in group C (all P<0.05), see **Table 2**.

Comparison of cardiovascular risk stratification

After 24 months of treatment, the cardiovascular risk stratification in the three groups was compared, and Kruskal-Wallis H test was used for the following pairwise comparison. The difference of risk stratification among the three groups was statistically significant (H=10.270, P=0.036). The risk stratification in group C was significantly different from that in group A (P=0.040) and group B (P=0.013), but there was no statistical significance between group A and group B (P=0.834). The results showed that the patients in group C had more severe cardiovascular risk stratification than those in groups A and B, as shown in **Table 3**.

Comparison of incidence of cardiovascular related diseases

After 24 months of treatment, the incidence of hyperglycemia and hypercholesterolemia in group C was significantly higher than that in groups A and B (P<0.05), as shown in **Table 4**.

Discussion

With the implementation of free antiviral therapy in China, the quality of life of HIV-infected patients has been greatly improved, and the life span has been prolonged. Therefore, adverse reactions of HAART drugs have attracted more and more attention [12]. HAART regimens consist of at least three different drugs, including nucleoside reverse transcriptase inhibitor (NRTI), protease inhibitor, and non-nucleoside reverse transcriptase inhibitor (NNRTI) [13]. There is no cure for HIV infection yet, but the immune function of patients can be maintained for decades by HAART. In recent years, clinical studies have pointed out that CVD is an important cause of death in HIV-infected

Table 4. Comparison of incidence rates of cardiovascular related diseases

Cardiovascular diseases	Group A (n=35)	Group B (n=40)	Group C (n=33)	χ^2	P
Overweight	4 (11.43)	6 (15.00)	7 (21.21)	1.252	0.535
Hypertension	5 (14.29)	3 (7.50)	6 (18.18)	1.909	0.385
Hyperglycemia	3 (8.57)	2 (5.00)	9 (27.27)*,#	8.836	0.012
Diabetes	1 (2.86)	0 (0)	3 (9.09)	4.294	0.117
Hypertriglyceridemia	6 (17.14)	7 (17.50)	10 (30.30)	2.301	0.316
Hypercholesterolemia	3 (8.57)	5 (12.50)	13 (39.39)*,#	12.144	0.002

Note: compared with group A, *P<0.05; compared with group B, #P<0.05.

patients [14]. Compared with healthy individuals, the host susceptibility of HIV patients, virus and antiviral drugs promote the development and progression of CVD. This study explored the correlation between different HAART regimens and cardiovascular risk factors to provide reference for the adoption of treatment schemes and relevant comprehensive interventions.

In this study, three combinations of HAART drug regimens were applied to three groups of patients respectively. Group A: lamivudine + zidovudine + nevirapine; Group B: lamivudine + tenofovir + efavirenz; Group C: lamivudine + tenofovir + LPV/r. Lamivudine is a nucleotide analogue that has competitive inhibition on the synthesis and extension of viral DNA chains [15]. Zidovudine, a NRTI, is phosphorylated to zidovudine triphosphate by thymidine kinase in virus-infected cells, which selectively inhibits HIV reverse transcriptase (HIV-RT), resulting in termination of HIV chain synthesis and preventing HIV replication [16]. Tenofovir refers to a novel NRTI that effectively resists various viruses and inhibits HIV replication by inhibiting the activity of HIV-RT [17]. Nevirapine is a NNRTI of HIV-1, which can bind directly to HIV-RT and block RNA- and DNA-dependent DNA polymerase activities by disrupting the enzyme's catalytic site [18]. Efavirenz, a selective NNRTI of HIV-1, acts on templates, primers or nucleoside triphosphates through non-competitive binding and inhibition of HIV-1 RT activity, along with a small part of competitive inhibition, thus preventing virus transcription and replication [19]. LPV/r belongs to protease inhibitor and is indicated for the treatment of HIV-1-infected adults and children over 2 years old in combination with other ARV drugs [20].

The results of this study showed that the $CD4^+$T lymphocyte count in the three groups increased significantly after 6, 12, and 24 months of treatment, while the count showed no significant difference among the three groups at each time point, suggesting that all three HAART regimens significantly improved the $CD4^+$T lymphocyte count of patients, with no significant difference in the therapeutic effects. After 24 months of treatment, all cardiovascular risk factors in the three groups were significantly different from those before treatment. Similar to a relevant report [5] that HAART might cause changes in cardiovascular related risk factors of the body, mainly manifesting as abnormalities in blood pressure, blood lipid, and blood glucose metabolism, as well as IMT thickening. Moreover, our study demonstrated that the changes of cardiovascular risk factors in Group C were more significant than those in Groups A and B. After 24 months of treatment, the cardiovascular risk stratification in Group C was severer than that in Groups A and B. The incidence of hyperglycemia and hypercholesterolemia in Group C was significantly higher than that in Groups A and B. These suggested that HAART treatment of lamivudine + tenofovir + lopinavir and ritonavir had a greater impact on cardiovascular risk factors and glucose and lipid metabolism of HIV-infected patients, and the risk of CVD was higher than combination of reverse transcriptase inhibitors. A similar conclusion was reached in other research [21] that abnormal fat distribution appeared in some patients after taking protease inhibitors for anti-HIV treatment. Specifically, some patients who took protease inhibitors continuously for three months or more had abnormal adipose tissue deposition at the bottom of the neck, without obvious changes in body weight. In addition, a study showed that protease inhibitors might affect metabolic function, causing an increase in the level of blood glucose and triglycerides, triggering insulin resistance and

diabetes [22]. However, due to the small sample size included in this study, some deviations may occur in the collected data. Therefore, the sample size will be further expanded in later studies to obtain more reliable clinical research data.

To sum up, HAART regimens effectively improve the $CD4^+$T lymphocyte level of patients and achieve reliable curative effects in treating HIV-infected patients. However, they may affect the changes of cardiovascular related risk factors of patient, in which the combined use of protease inhibitors has a more serious impact on the body metabolism and poses a greater risk of CVD, requiring the attention of clinical workers.

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Disclosure of conflict of interest

None.

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References

[1] Koochak HE, Babaii A, Pourdast A, Golrokhy R, Rasoolinejad M, Khodaei S, Moghadam SRJ, Taheri RR and Seyed Alinaghi SA. Prevalence of adverse drug reactions to highly active antiretroviral therapy (HAART) among HIV-positive patients in imam khomeini hospital of Tehran, Iran. Infect Disord Drug Targets 2017; 17: 116-119.

[2] Kim MJ, Chang HH, Kim SI, Kim YJ, Park DW, Kang C, Kee MK, Choi JY, Kim SM, Choi BY, Kim WJ, Kim JM, Choi JY, Choi YH, Lee JS and Kim SW; Korea HIV/AIDS Cohort Study. Trend of CD4+ cell counts at diagnosis and initiation of highly active antiretroviral therapy (HAART): Korea HIV/AIDS cohort study, 1992-2015. Infect Chemother 2017; 49: 101-108.

[3] Politch JA, Mayer KH and Anderson DJ. HIV-1 is undetectable in preejaculatory secretions from HIV-1-infected men on suppressive HAART. AIDS 2016; 30: 1899-903.

[4] Baynes HW, Tegene B, Gebremichael M, Birhane G, Kedir W and Biadgo B. Assessment of the effect of antiretroviral therapy on renal and liver functions among HIV-infected patients: a retrospective study. HIV AIDS (Auckl) 2017; 9: 1-7.

[5] Logerot S, Rancez M, Charmeteau-De MB, Figueiredo-Morgado S, Rozlan S and Tambussi G. HIV reservoir dynamics in HAART-treated poor immunological responder patients under IL-7 therapy. Aids 2018; 32: 1.

[6] Gibson TM, Morton LM, Shiels MS, Clarke CA and Engels EA. Risk of non-Hodgkin lymphoma subtypes in HIV-infected people during the HAART era: a population-based study. AIDS 2014; 28: 2313-2318.

[7] Efficacy and safety of highly active antiretroviral therapy for AIDS patients. The Chinese Journal of Clinicall Pharmacology 2017; 33: 1618-1620.

[8] Portela MB, Lima de Amorim E, Santos AM, Alexandre da Rocha Curvelo J, de Oliveira Martins K, Capillé CL, Maria de Araújo Soares R and Barbosa de Araújo Castro GF. Candida species from oral cavity of HIV-infected children exhibit reduced virulence factors in the HAART era. Microb Pathog 2017; 102: 74-81.

[9] de Paula Menezes R, de Melo Riceto ÉB, Borges AS, de Brito Röder DV and dos Santos Pedroso R. Evaluation of virulence factors of Candida albicans isolated from HIV-positive individuals using HAART. Arch Oral Biol 2016; 66: 61-65.

[10] Daniele P. Diagnosis and treatment of AIDS onset. Europe PMC 1999.

[11] Zhu HM, Wang DH, Shi JH, Kong HX, Li YJ and Li HJ. Relationship between coronary artery calcification and chemokines and epicardial adipose tissue in patients with maintenance hemodialysis. Chinese Journal of Arteriosclerosis 2018; 26.

[12] Matinella A, Lanzafame M, Bonometti MA, Gajofatto A, Concia E, Vento S, Monaco S and Ferrari S. Neurological complications of HIV infection in pre-HAART and HAART era: a retrospective study. J Neurol 2015; 262: 1317-1327.

[13] Batman PA, Kapembwa MS, Belmonte L, Tudor G, Kotler DP, Potten CS, Booth C, Cahn P and Griffin GE. HIV enteropathy: HAART reduces HIV-induced stem cell hyperproliferation and crypt hypertrophy to normal in jejunal mucosa. J Clin Pathol 2014; 67: 14.

[14] Kallianpur AR, Wang Q, Jia P, Hulgan T, Zhao Z, Letendre SL, Ellis RJ, Heaton RK, Franklin DR, Barnholtz-Sloan J, Collier AC, Marra CM, Clifford DB, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA and Grant I; CHARTER Study Group. Anemia and red cell

indices predict HIV-associated neurocognitive impairment in the HAART era. J Infect Dis 2015; 213: 1065.

[15] Rey D, Treger M, Sibilia J, Priester M, Bernard-Henry C, Cheneau C and Javier RM. Bone mineral density changes after 2 years of ARV treatment, compared to naive HIV-1-infected patients not on HAART. Infect Dis (Lond) 2015; 47: 1-8.

[16] Tamí-Maury IM, Willig JH, Jolly PE, Vermund S, Aban I, Hill JD, Wilson CM and Kempf MC. Prevalence, incidence, and recurrence of oral lesions among HIV-infected patients on HAART in Alabama: a two-year longitudinal study. South Med J 2015; 104: 561.

[17] Chitra P, Bakthavatsalam B and Palvannan T. Osteonecrosis with renal damage in HIV patients undergoing HAART. Biomed Pharmacother 2014; 68: 881-885.

[18] Ballocca F, Gili S, D'Ascenzo F, Marra WG, Cannillo M, Calcagno A, Bonora S, Flammer A, Coppola J, Moretti C and Gaita F. HIV infection and primary prevention of cardiovascular disease: lights and shadows in the HAART era. Prog Cardiovasc Dis 2016; 58: 565-576.

[19] Lipshultz SE, Wilkinson JD, Thompson B, Cheng I, Briston DA, Shearer WT, Orav EJ, Westphal JA, Miller TL and Colan SD; CHAART-2 Investigator Group. Cardiac effects of highly active antiretroviral therapy in perinatally HIV-infected children: the CHAART-2 study. J Am Coll Cardiol 2017; 70: 2240.

[20] D'Ascenzo F, Cerrato E, Calcagno A, Grossomarra W, Ballocca F, Omedè P, Montefusco A, Veglia S, Barbero U, Gili S, Cannillo M, Pianelli M, Mistretta E, Raviola A, Salera D, Garabello D, Mancone M, Estrada V, Escaned J, De Marie D, Abbate A, Bonora S, Zoccai GB, Moretti C and Gaita F. High prevalence at computed coronary tomography of non-calcified plaques in asymptomatic HIV patients treated with HAART: a meta-analysis. Atherosclerosis 2015; 240: 197-204.

[21] Bulteel N, Bansi-Matharu L, Churchill D, Dunn D, Bibby D, Hill T, Sabin C and Nelson M; UK Collaborative HIV Cohort (CHIC) Study Group; UK HIV Drug Resistance Database (UK HDRD) Study Group. The emergence of drug resistant HIV variants at virological failure of HAART combinations containing efavirenz, tenofovir and lamivudine or emtricitabine within the UK Collaborative HIV Cohort. J Infect 2014; 68: 77-84.

[22] Landay A, Golub ET, Desai S, Zhang J, Winkelman V, Anastos K, Durkin H, Young M, Villacres MC, Greenblatt RM, Norris PJ and Busch MP; Women's Interagency HIV Study. HIV RNA levels in plasma and cervical-vaginal lavage fluid in elite controllers and HAART recipients. AIDS 2014; 28: 739.