Journal of Medical and Biomedical Sciences (2016) 5(3): 13-27

doi: http://dx.doi.org/10.4314/jmbs.v5i3.2

ORIGINAL ARTICLE

Evaluation of HIV therapeutic agents on immunological, lipid and lipoprotein indices in Ghanaian HIV-1 infected patients

L. Quaye[1], W.K.B.A Owiredu[2], N. Amidu[1], Y. Adams[1] and A.W. Huseini[1]

[1]Department of Biomedical Laboratory Science, School of Allied Health Sciences, University for Development Studies, Tamale, Ghana, [2]Department of Molecular Medicine, School of Medical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

HIV-1 infected patients initiating antiretroviral therapy (ART) in Ghana are placed on one of the two most commonly used non-nucleoside reverse transcriptase inhibitors (NNRTIs), nevirapine (NVP) and efavirenz (EFV), in combination with a nucleoside reverse transcriptase inhibitor backbone of either combivir (CBV) or stavudine (d4T)/lamivudine (3TC). This study sought to evaluate the effect of these therapeutic agents on weight, immunological, lipid and lipoprotein changes as well as the atherogenic indices of Ghanaian HIV-1 infected patients. This observational study was carried out at the ART clinic of the Regional Hospital, Bolgatanga in the Upper-East region of Ghana from September 2008 to September 2009 comprising 61 HIV-1 infected patients who were initiated on NVP or EFV in combination with either CBV or d4T/3TC. Out of the 61 enrolled patients, 27(44.3%) were on NVP and 34(55.7%) were on EFV. Within the NVP group, 16 (59.3%) were on CBV and 11(40.7%) on d4T/3TC whilst the EFV group had 26(76.5%) on CBV and 8 (23.5%) on d4T/3TC. Percentage changes in lipid profile components comprising total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-c) and low density lipoprotein cholesterol (LDL-c) was assessed over the 12-month period. Percentage changes in atherogenic index expressed as TC/HDL-c and LDL-c/HDL-c was also estimated. NVP elicited a 10.2% increase in weight compared to EFV and this was associated with CBV combination use. EFV further elicited a 9.1% increase in TC, 1.2% increase in TG, 39.3% increase in LDL-c and a 4.1% increase in HDL-c which resulted in concomitant percentage increases in TC/HDL-c (22%) and LDL-c/HDL-c (47.3%). CBV as a NRTI component of EFV elicited a 4.3% increase in TC/HDL-c and a 16.6% increase in LDL-c/HDL-c compared to d4T/3TC whilst conversely, d4T/3TC elicited a 3.6% increase in TC/HDL-c and a 34.0% when used in combination with NVP. NVP combination therapy elicited improvement in weight compared to EFV combination therapy for the different categories of patients. The less atherogenic lipid profile observed in patients taking NVP in comparison to those taking EFV and the reduction in CHD risk associated with NVP + CBV combination therapy observed in this study should be factored into considerations taken when selecting the most appropriate ART regimen for treatment naïve HIV-1 infected patients.
Journal of Medical and Biomedical Sciences (2016) 5(3), 13-27

Keywords: HIV-1, Antiretroviral therapy, Immunological, Lipids, Atherogenic indices, Bolgatanga, Ghana

INTRODUCTION

Highly active antiretroviral therapy (HAART) has decreased morbidity and mortality associated with human immunodeficiency virus (HIV) infection in those for whom it is available (Palella *et al.*, 1998; Stebbing *et al.*, 2004). In the face of such benefits of combination therapy which have revolutionalized the care of patients with HIV-1 infection, increasingly severe treatment-associated metabolic abnormalities have been observed, among them dyslipidaemia, insulin resistance and overt diabetes which are well-known risk factors for cardiovascular disease (Carr *et al.*, 1999; Carr and Cooper, 2000). These side effects may increase the risk of premature myocardial infarction, although direct evidence of such an association is inconsistently reported in existing literature (Henry *et al.*, 1998;

Correspondence: *Dr. Nafiu Amidu, Department of Biomedical Laboratory Science, School of Allied Health Sciences, UDS, Tamale, Ghana*
Email: anafiu@uds.edu.gh

Klein and Hurley, 2003).

Numerous studies have demonstrated that patients using protease inhibitor (PI) – based antiretroviral therapy (ART) develop atherogenic changes in their lipoprotein profile consisting of elevations in triglyceride-rich lipoproteins, total cholesterol and low density lipoprotein cholesterol (LDL-c) (Bonnet *et al.*, 2000; Bozzette *et al.*, 2003). Tashima *et al.,* (1999) showed that with efavirenz-based regimen total cholesterol (TC) and high density lipoprotein-cholesterol (HDL-c) tended to rise after 48 weeks of treatment.

A nevirapine-based regimen in treatment-naïve patients after 24 weeks of treatment led to a prominent increase in HDL-c accompanied by an increase in apolipoprotein-AI and a decrease in the ratio of TC to HDL-c (van der Valk *et al.*, 2001). This effect on HDL-c was sustained after 96 weeks of treatment (van der Valk *et al.*, 2001). With such differences in ART regimen, several randomized clinical trials in ART-naïve patients have shown that non-nucleoside reverse transcriptase inhibitors (NNRTI's) are as effective as regimen that includes PI's (Staszewski *et al.*, 1999; Podzamczer *et al.*, 2002).

The use of NNRTI-based ART as the first choice regimen has become increasingly popular for reasons such as lower pill burden and perceived low toxicity associated with PI-based regimen. NNRTI-based regimen do not necessitate any restrictions on food intake and as such they contribute to better adherence to therapy by the patients, which is crucial for a sustained effect of treatment (Flandre *et al.*, 2002; Mannheimer *et al.*, 2002).

The two most used NNRTI drugs are nevirapine (NVP) and efavirenz (EFV) with several large cohort studies suggesting that EFV is more effective than NVP (Cozzi-Lepri *et al.*, 2002; Matthews *et al.*, 2002). In Ghana, the use of triple drug therapy consisting of a combination of two nucleoside analogues with PI's or a non-nucleoside inhibitor analogue is currently prescribed but there is paucity of data on a comparative study about their effect on serum lipid profiles. This study therefore sought to assess the impact of antiretroviral drugs on weight, immunological, lipid and lipoprotein changes in order to improve the management of HIV-1 infected patients.

MATERIALS AND METHODS

Study site and participant selection

This observational study was carried out at the antiretroviral (ART) clinic of the Regional Hospital, Bolgatanga in the Upper-East region of Ghana from September 2008 to September 2009 with approval from the Clinical Coordination and Research Development Board of the hospital. All human immunodeficiency virus-1 (HIV-1) infected patients who were at least 18 years or more and who have received adherence and dietary counselling and were ready to start antiretroviral (ARV) therapy at the clinic at the time of the study period were eligible for enrolment in the study.

HIV-1 infected patients who had tuberculosis (TB) infection and were on TB medication, patients who were on vitamin supplements and antibiotics, female patients who were found to be pregnant and patients who had adverse events during the course of the study were excluded from the study. All the study participants provided written informed consent before enrolment into the study.

Drug administration

Patients enrolled in the study were initiated on nevirapine (NVP) or efavirenz (EFV)–based highly active antiretroviral therapy (HAART) with one (1) of two (2) backbone nucleoside reverse transcriptase inhibitor (NRTI) combinations: Combivir (CBV) – a co-formulation of [zidovudine (ZDV) + lamivudine (3TC)] or stavudine (d4T)/lamivudine (3TC).

Dosing:

Nevirapine– was administered as 200 mg once daily dose for the first two (2) weeks and then 200 mg twice daily for the period of the study.

Efavirenz– was administered as 600 mg once daily dose for the period of the study.

Combivir– a co-formulated drug of zidovudine (300 mg) and lamivudine (150 mg) was administered to the patients (weight ≥30 kg) at one (1) tablet twice daily for the period of the study.

Lamivudine – was administered as 150 mg twice daily dose for the period of the study.

Stavudine– was administered as 30 mg twice daily dose (if the weight of the patient is <60 kg) or 40 mg twice daily for the period of the study.

Assessments
Blood samples and weight for each of the patients was taken at the initiation of therapy (baseline), six (6) months and one (1) year after therapy. Adherence to treatment and adverse drug events in the patients were assessed at the follow-up periods by self-report. Out of a total of 90 HIV-1 infected patients enrolled in the study at baseline, 7 reported of adverse drugs events, 9 declined participations in the course of the study period and 13 were lost to follow -up leaving complete set of data for 61 patients at the end of the study period.

Sampling
Five (5) ml of blood sample was taken aseptically from the antecubital vein of the patients after an overnight fast (12-16 hours) at baseline, 6 months and 12 months. Three millilitres (3 ml) of the blood was dispensed into vacutainer® plain tube and allowed to clot. The clotted sample was then centrifuged at 3000 rpm for 10 minutes and the sera aliquoted into sterile cryovials and stored at -80^{o}C until assay for lipid profile analysis was conducted. The remaining 2 ml of the blood sample was put into vacutainer ethylene diaminetetraacetic acid (EDTA) tubes and used for CD_4 counts.

Lipid Profile and Immunological assays
Fasting serum total cholesterol (TC), triglycerides (TG) and high density lipoprotein cholesterol (HDL-c) were estimated with the ATAC® 8000 Random Access Chemistry analyzer (Elan Diagnostics, Smithfield, CA, USA) using the reagent manufacturer's (JAS diagnostics Inc.) instructions. Low density lipoprotein cholesterol (LDL-c) was estimated using the Friedewald equation (Friedewald *et al.*, 1972) and the concentration of very low density lipoprotein (VLDL) (mmol L^{-1}) was calculated as TG/2.2 according to Friedewald *et al.,* (1972). Atherogenic indices were calculated as TC/HDL-c and LDL-c/HDL-c ratios. Absolute cell count of CD_4 T-lymphocytes in non-haemolyzed whole blood was estimated with the BD FACScount system (Becton Dickenson and Company, California, USA).

Weight
The weight of the patients was measured to the nearest 0.1 kg in light clothing at baseline, 6 months and 12 months of the study period on a bathroom scale (Zhongshan Camry Electronics Co. Ltd. Guangdong, China).

Outcome measurements
The mean percentage changes in TC, TG, HDL-c, VLDL, LDL-c, TC/HDL-c and LDL-c/HDL-c ratios at baseline (Month 0) and one year (Month 12) after start of treatment were determined for each patient based on the combination therapy using the Van Leth *et al.,* (2004) formula:

$$\text{Percent change } (\%) = \frac{\text{Concentration at month 12} - \text{Concentration at month 0}}{\text{Concentration at month 0}} X\ 100$$

Statistical analysis
Results are presented as means ± SD and proportions. Student's *t*-test was used to compare the statistical significance of all continuous variables. The Chi-square test statistic was used to compare the statistical significance of all categorical variables. A p-value < 0.05 was considered to be statistically significant. All statistical analyses were performed using GraphPad Prism version 5.00 for windows (GraphPad software, San Diego California USA, www.graphpad.com).

RESULTS

General characteristic of the studied population
The general characteristics of the study population at baseline (month 0) and one year (month 12) after

Table 1: General characteristics of the study group at baseline (Month 0) and 1 year (Month 12) after HAART

	Month 0				Month 12				
Parameters	**Total(n=61)**	**Male(n=15)**	**Female(n=46)**	**Total(n=61)**	**Male(n=15)**	**Female(n=46)**	**p**	**p***	**p****
Age (years)	34.8±8.4	35.5±7.0	34.5±8.9	♣	♣	♣	♣	♣	♣
Weight (kg)	49.8±7.8	53.3±10.4	48.7±6.5	51.9±8.5	54.7±8.7	50.9±8.4	0.172	0.603	0.159
CD_4 (cells mm^{-3})	259.3±136.9	233.1±149.8	267.9±133.1	272.1±124.4	240.6±122.7	282.3±124.6	0.592	0.881	0.593
CD_4 classification									
<200	18(29.5)	6(40.0)	12(26.1)	18(29.5)	5(33.3)	13(28.3)	1.000	0.705	0.815
200 - 499	39(63.9)	8(53.3)	31(67.4)	41(67.2)	10(66.7)	31(67.4)	0.703	0.456	1.000
>500	4(6.6)	1(6.7)	3(6.5)	2(3.3)	0(0.0)	2(4.3)	0.402	0.309	0.646
Lipid Profile ($mmolL^{-1}$)									
TC	3.2±1.0	3.0±0.6	3.3±1.0	3.6±0.8	3.2±0.8	3.7±0.8	0.012	0.334	0.018
TG	1.6±0.7	1.5±0.4	1.6±0.7	1.6±0.4	1.6±0.4	1.7±0.5	0.522	0.603	0.389
HDL-c	1.0±0.4	0.9±0.3	1.1±0.4	1.1±0.4	1.0±0.4	1.1±0.4	0.503	0.858	0.509
VLDL	0.7±0.3	0.6±0.2	0.7±0.3	0.7±0.2	0.7±0.2	0.7±0.2	0.519	0.608	0.387
LDL-c	1.4±0.8	1.3±0.5	1.4±0.9	1.8±0.8	1.5±0.9	1.9±0.8	0.008	0.480	0.009
Atherogenic Index									
TC/HDL	3.4±1.3	3.3±1.2	3.4±1.4	3.8±1.8	3.8±2.1	3.8±1.7	0.183	0.496	0.259
LDL-c/HDL	1.6±1.1	1.6±1.1	1.6±1.2	2.0±1.4	1.9±1.7	2.0±1.3	0.081	0.470	0.112

Data are presented as mean ± SD and proportions; p - level of significance when total at month 0 was compared to total at month 12 (paired t-test); p*- level of significance when male at month 0 was compared to male at month 12; p**- the level of significance when female at month 0 was compared to female at month 12; TC–total cholesterol; TG–triglycerides; HDL-c–high density lipoprotein cholesterol; VLDL–very low density lipoprotein; LDL-c– low density lipoprotein cholesterol; ♣- no p-values calculated/no change in calculated values at month 12.

treatment with antiretrovirals (ARV's) are summarized in Table 1. Out of 61 HIV-1 infected patients with a mean age of 34.8 ± 8.4 years followed for a period of one year, 15 (24.6%) were males with a mean age of 35.5 ± 7.0 years and 46 (75.4%) were females with a mean age of 34.5 ± 8.9 years. Increases in the weight and mean CD_4 counts in the study participants after one year of treatment showed no statistically significant differences. A further stratification of the study participants based on CD_4 counts using the Centre for Disease Control (CDC) criteria at baseline and month 12 showed no statistically significant differences in the proportion of patients within the three defining groups.

Lipid profile analyses showed significant increases in the mean total cholesterol (TC) concentration of the study participants at baseline (3.2 ± 1.0 $mmolL^{-1}$) and at month 12 (3.6 ± 0.8 $mmolL^{-1}$) (p = 0.012) with the same trend being observed in the female patients (3.3 ± 1.0 $mmolL^{-1}$ and 3.7 ± 0.8 $mmolL^{-1}$ respectively) (p = 0.018). Increases in the mean concentration of low density lipoprotein cholesterol (LDL-c) in the study participants at baseline (1.4 ± 0.8 $mmolL^{-1}$) and month 12 (1.8 ± 0.8 $mmolL^{-1}$) (p = 0.008) and in the female patients (1.4 ± 0.9 $mmolL^{-1}$ and 1.9 ± 0.8 $mmolL^{-1}$ respectively) (p = 0.009) were statistically significant. No significant differences were however observed in the mean concentrations of triglycerides (TG) and high density lipoprotein cholesterol (HDL-c) after one year of treatment. Increases in the atherogenic indices defined by TC/HDL-c and LDL-c/HDL-c ratios after one year of treatment also showed no statistically significant differences.

Parameter changes when stratified by NNRTI& NRTI use

The general distribution of age, sex, weight and CD_4 counts of the study participants stratified by the type of non-nucleoside reverse transcriptase inhibitor (NNRTI) (NVP or EFV) and the specific nucleoside reverse transcriptase inhibitor (NRTI) backbone (CBV or d4T/3TC) being used are presented in Tables 2 and 3. Out of a total of 61 study participants, 27 (44.3%) were on a daily dose of

Table 2: Characteristics of the nevirapine group stratified by specific NRTI backbone

	Total (n = 27)			CBV (n = 16)			d4T/3TC (n = 11)		
Parameters	**Month 0**	**Month 12**	**p value**	**Month 0**	**Month 12**	**p value**	**Month 0**	**Month 12**	**p value**
Male	5(18.5)	♣		2(12.5)	♣		3(27.3)	♣	
Female	22(81.5)	♣		14(87.5)	♣		8(72.7)	♣	
Age (years)	32.3±6.7	♣		34.6±5.6	♣		28.9±6.6	♣	
Weight (kg)	48.6± 4.4	53.4±8.2	0.010	48.7±3.3	54.5±7.0	0.006	48.5±5.9	51.7±9.8	0.353
CD_4 (cells mm^{-3})	270.8±115.0	291.0±127.3	0.542	280.2±130.3	297.9±137.3	0.711	257.1±92.8	281.1±116.9	0.599
CD_4 classes									
<200	5(18.5)	7(25.9)	0.513	4(25.0)	4(25.0)	1.000	1(9.1)	3(27.3)	0.269
200-499	21(77.8)	18(66.7)	0.362	11(68.8)	11(68.8)	1.000	10(90.9)	7(63.6)	0.127
>500	1(3.7)	2(7.4)	0.553	1(6.3)	1(6.3)	1.000	0(0.0)	1(9.1)	0.306

Data are presented as means ± SD and proportions; p-value defines the level of significance when month 0 was compared to month 12 (paired t-test); NVP-nevirapine; CBV-combivir; d4T-stavudine and 3TC-lamivudine; ♣-no change in data distribution at month 12.

Table 3: Characteristics of the efavirenz group stratified by specific NRTI backbone

	Total (n = 34)			CBV (n = 26)			d4T/3TC (n = 8)		
Parameters	**Month 0**	**Month 12**	**p value**	**Month 0**	**Month 12**	**p val-ue**	**Month 0**	**Month 12**	**p value**
Male	10(29.4)	♣		9(34.6)	♣		1(12.5)	♣	
Female	24(70.6)	♣		17(65.4)	♣		7(87.5)	♣	
Age (years)	36.8±9.3	♣		35.3±8.3	♣		41.5±11.3	♣	
Weight (kg)	50.8±9.6	50.7±8.7	0.943	51.1±10.34	51.1±8.6	1.000	49.9±7.1	49.3±9.6	0.885
CD4 (cells mm-3)	250.3±153.2	257.0±121.9	0.842	265.6±154.8	264.3±126.7	0.974	200.5±146.0	233.3±108.9	0.619
CD4 class									
<200	13(38.2)	11(32.4)	0.612	8(30.8)	8(30.8)	1.000	5(62.5)	3(37.5)	0.317
200-499	18(52.9)	23(67.6)	0.215	16(61.5)	18(69.2)	0.559	2(25.0)	5(62.5)	0.131
>500	3(8.8)	0(0.0)	0.077	2(7.7)	0(0.0)	0.149	1(12.5)	0(0.0)	0.302

Data are presented as means ± SD and proportions; p-value defines the level of significance when month 0 was compared to month 12 (paired t-test); ♣-no change in data distribution at month 12.

nevirapine (Table 2) and 34 (55.7%) were on a daily dose of efavirenz (Table 3). In the NVP group, 16 (59.3%) were on CBV and 11 (40.7%) were on d4T/3TC as NRTI backbone of the combination therapy while the EFV group had 26 (76.5%) patients on CBV and 23.5% patients on d4T/3TC. Females outnumbered males by 4 to 1 in the nevirapine group whilst the ratio in the efavirenz group was 2 to 1 making the study participants predominantly female.

From a baseline weight of 48.6 ± 4.4 kg, there was a significant increase in weight (53.4 ± 8.2 kg) ($p = 0.010$) in patients on NVP after one year of treatment. A further analysis by type of NRTI being used showed significant increase in weight (48.7±3.3 to 54.5±7.0; $p = 0.006$) in patients on CBV while patients on d4T/3TC showed no significant changes in weight ($p = 0.353$). Conversely, no significant change in weight was observed in the EFV group after one year of treatment and likewise when examined by NRTI use. Increases in mean CD_4 counts and the distribution of patients by CD_4 into the three groups defined by the CDC in the NVP and EFV groups after one year of treatment showed no statistical significant differences.

Changes in lipid and lipoproteins

Lipid profile changes and atherogenic indices of the study participants on NVP and EFV at baseline and one year after treatment are presented in the Table 4. The mean concentration of TC in patients on EFV at baseline (2.9 ± 0.9 mmol L^{-1}) significantly increased after one year of treatment (3.5 ± 0.7 mmol L^{-1}) ($p = 0.018$; $\%\Delta = 24.2$) while the mean TC concentration in patients on NVP showed no significant change ($p = 0.214$). Of the two drug classes, EFV caused a mean TC increase of 9.5% when compared to NVP but a comparison of the percentage changes showed no statistical significance ($p = 0.329$). The mean LDL-c concentration in patients on EFV also increased significantly from a baseline value of 1.3 ± 0.7 mmol L^{-1} to 1.8 ± 0.7 mmol L^{-1} ($p = 0.006$; $\%\Delta = 53.1$) while that of patients on NVP showed no statistical significant difference. EFV caused a 39.3% increase in LDL-c concentration compared to NVP but a comparison of the percentage changes within

Table 4: Percentage change in lipid concentrations, weight and CD_4 in the study group stratified by NNRTI use

	NVP (n = 27)				EFV (n = 34)					
Parameters	**Month 0**	**Month 12**	**%Δ**	**p-value**	**Month 0**	**Month 12**	**%Δ**	**p-value**	**Difference in % Δ (NVP-EFV)**	**p-value of %Δ (NVP & EFV)**
Lipid Profile (mmol L^{-1})										
TC	3.5 ± 1.0	3.8 ± 1.0	14.7	0.214	2.9 ± 0.9	3.5 ± 0.7	24.2	0.018	-9.5	0.329
TG	1.7 ± 0.6	1.7 ± 0.4	4.6	0.673	1.6 ± 0.7	1.6 ± 0.5	5.8	0.633	-1.2	0.893
HDL-c	1.2 ± 0.3	1.3 ± 0.3	13.7	0.292	0.9 ± 0.4	1.0 ± 0.4	17.8	0.883	-4.1	0.793
VLDL	0.8 ± 0.3	0.8 ± 0.2	4.6	0.667	0.7 ± 0.3	0.7 ± 0.2	5.8	0.633	-1.2	0.893
LDL-c	1.5 ± 0.8	1.8 ± 1.0	13.8	0.302	1.3 ± 0.7	1.8 ± 0.7	53.1	0.006	-39.3	0.430
Atherogenic Index										
TC/HDL-c	3.1 ± 1.1	3.2 ± 1.0	7.8	0.530	3.6 ± 1.5	4.2 ± 2.2	29.8	0.146	-22.0	0.122
LDL-C/HDL-c	1.4 ± 0.9	1.5 ± 0.9	21.7	0.655	1.7 ± 1.3	2.3 ± 1.6	69.0	0.075	-47.3	0.354
Others										
Weight (kg)	48.6 ± 4.4	53.4 ± 8.2	10.2	0.010	50.8 ± 9.6	50.7 ± 8.7	1.1	0.943	9.1	0.029
CD_4 (cells mm^{-3})	270.8 ± 115.0	291.0 ± 127.3	13.4	0.542	250.3 ± 153.2	257.0 ± 121.9	14.2	0.842	-0.8	0.939

Data are presented as mean ± SD; Month 0 – baseline; %Δ – percentage change; p-value defines the level of significance when baseline was compared to month 12 (paired t-test) and p-value of %Δ defines the level of significance when %Δ of NVP was compared to %Δ of EFV (Unpaired t-test).

the two drug classes showed no statistical significance (p = 0.430). A 1.2% increase in TG concentration, 4.1% increase in HDL-c concentration and 1.2% increase in VLDL concentration were observed in patients on EFV compared to those on NVP but a comparison of the percentage changes between the two drug classes showed no statistical significance.

The atherogenic indices defined by TC/HDL-c and LDL-c/HDL-c ratios increased by 22.0% and 47.3% respectively in patients on EFV compared with those on NVP but a comparison of the percentage changes between the two drug classes showed no statistical significance (Table 4).

As showed in table 4, a 10.2% statistically significant increase in weight was observed in patients on NVP compared to a 1.1% increase in patients on EFV and a comparison of the percentage changes was statistically significant (p = 0.025).

Changes in lipid and lipoproteins by NRTI component in the NVP group

Analysis of the impact of NRTI's (CBV and d4T/3TC) in lipid and lipoprotein changes in the NVP group is shown in Table 5. CBV elicits a 1.8% increase in TC concentration and a 10.0% increase in HDL-c compared to d4T/3TC combination therapy but a comparison of the percentage changes between the two NRTI's was not statistically significant. d4T/3TC combination therapy on the other hand elicited a 2.9% increase in TG and VLDL concentrations and a 36.9% increase in LDL-c concentration compared to CBV therapy. A comparison of the difference in percentage changes however showed no statistical significance.

Atherogenic indices by NRTI component

The atherogenic indices defined by TC/HDL-c and LDL-c/HDL-c ratios increased by 3.6% and 34.0% respectively for patients on a d4T/3TC combination therapy compared to a CBV therapy but a comparison of the percentage differences within the two NRTI's showed no statistical significance (Table 5).

Changes in lipid and lipoproteins by NRTI

Table 5: Percentage change in lipid concentrations in study subjects on nevirapine (NVP) stratified by NRTI use

	CBV (16)				d4T/3TC (11)				Difference in	p-value of
Parameters	**Month 0**	**Month 12**	**%Δ**	**p value**	**Month 0**	**Month 12**	**%Δ**	**p value**	**%Δ**	**%Δ**
Lipid Profile (mmol L-1)										
TC	3.7 ± 1.1	4.0 ± 1.0	15.5	0.422	3.3 ± 0.6	3.6 ± 0.9	13.7	0.3	1.8	0.9
TG	1.7 ± 0.6	1.7 ± 0.4	3.4	0.588	1.7 ± 0.6	1.7 ± 0.5	6.3	0.987	-2.9	0.83
HDL-c	1.2 ± 0.4	1.3 ± 0.4	17.8	0.389	1.1 ± 0.2	1.2 ± 0.2	7.8	0.527	10	0.5
VLDL	0.7 ± 0.3	0.7 ± 0.2	3.4	0.584	0.8 ± 0.3	0.8 ± 0.2	6.3	0.992	-2.9	0.83
LDL-c	1.7 ± 1.0	1.9 ± 1.0	26	0.472	1.4 ± 0.6	1.7 ± 0.9	62.9	0.382	-36.9	0.372
Atherogenic Index										
TC/HDL-c	3.2 ± 1.3	3.2 ± 1.0	6.3	0.895	2.9 ± 0.6	3.2 ± 0.9	9.9	0.627	-3.6	0.817
LDL-c/HDL-c	1.5 ± 1.1	1.6 ± 0.9	22.9	0.906	1.3 ± 0.6	1.5 ± 0.9	56.9	0.518	-34	0.42

Data are presented as means ± SD; p-value defines the level of significance when mean concentrations at Month 0 was compared to that at Month 12.

Table 6: Percentage change in lipid concentrations in study subjects on efavirenz (EFV) and specific NRTI's

Parameters	CBV (26)				d4T/3TC (8)				Difference in %Δ	p-value of %Δ
	Month 0	Month 12	%Δ	p value	Month 0	Month 12	%Δ	p value		
Lipid Profile (mmol L^{-1})										
TC	2.9 ± 1.0	3.5 ± 0.8	25.5	0.046	3.0 ± 0.8	3.4 ± 0.4	19.9	0.173	5.6	0.725
TG	1.6 ± 0.8	1.6 ± 0.4	5.2	0.525	1.5 ± 0.6	1.6 ± 0.5	7.9	0.832	-2.7	0.860
HDL-c	0.9 ± 0.4	1.0 ± 0.4	11.5	0.930	0.8 ± 0.4	0.9 ± 0.4	38.4	0.890	-26.9	0.368
VLDL	0.7 ± 0.4	0.7 ± 0.2	5.2	0.525	0.7 ± 0.3	0.7 ± 0.2	7.9	0.832	-2.7	0.860
LDL-c	1.2 ± 0.8	1.8 ± 0.7	48.2	0.013	1.4 ± 0.6	1.8 ± 0.7	40.4	0.256	7.8	0.907
Atherogenic Index										
TC/HDL-c	3.5 ± 1.5	4.1 ± 2.3	26.7	0.207	4.0 ± 1.6	4.6 ± 2.0	22.4	0.490	4.3	0.623
LDL-c/HDL-c	1.8 ± 1.3	2.2 ± 1.6	44.4	0.106	2.1 ± 1.3	2.6 ± 1.6	27.8	0.473	16.6	0.650

Data are presented as means ± SD; p-value defines the level of significance when mean concentrations at Month 0 was compared to that at Month 12.

component in the EFV group

In the EFV group, CBV elicited a 25.5% significant increase in TC concentration and a 48.2% significant increase in LDL-c concentration. A comparison of the percentage changes within the two NRTI's however showed no statistical significance. d4T/3TC combination therapy increased TG and VLDL concentrations by 2.7% respectively and HDL-c concentration by 26.9% when compared to a combination therapy of CBV but a comparison of the percentage changes showed no statistical significance (Table 6).

Atherogenic Indices by NRTI component

As shown in table 6, a CBV combination therapy increases TC/HDL-c ratio by 4.3% and LDL-c/HDL-c by 16.6% when compared to the d4T/3TC therapy. The percentage changes however did not show any statistically significant differences when compared.

Effect of gender and CD_4 counts on lipid and lipoprotein concentration

An analysis of the association of sex and CD_4 counts with changes in lipid (TC, TG, HDL-c, VLDL, and LDL-c) concentrations and atherogenic indices (TC/HDL and LDL-c/HDL) are presented in Tables 7 and 8. The percentage changes in TC and HDL-c concentrations were increased in females compared to males. Contrarily, the percentage changes in TG, VLDL and LDL-c concentrations were increased in males compared to females. A comparison of all the percentage changes between both sexes however showed no statistically significant differences. Likewise, the atherogenic indices as defined by TC/HDL-c and LDL-c/HDL-c concentrations were increased in males with no statistically significant difference between the percentage changes.

CD_4 counts of <200 cells mm^{-3} was associated with increased percentage changes in TG, VLDL, LDL-c concentrations and the atherogenic indices defined by TC/HDL-c and LDL-c/HDL-c in comparison to CD_4 counts be-

Table 7: Analysis of some factors associated with percentage changes in lipid (TC, TG and HDL-C) concentrations

	TC			TG			HDL-c		
Variables	**M0**	**M12**	**% Δ**	**M0**	**M12**	**% Δ**	**M0**	**M12**	**% Δ**
Sex									
Male	3.0 ± 0.6	3.2 ± 0.8	14.3	1.5 ± 0.4	1.6 ± 0.4	9.8	0.9 ± 0.3	1.0 ± 0.4	10.8
Female	3.3 ± 1.0	3.8 ± 0.8	21.9	1.6 ± 0.7	1.7 ± 0.5	3.8	1.1 ± 0.4	1.1 ± 0.4	17.7
p-value			0.499			0.574			0.696
CD_4 (cells mm^{-3})									
<200	3.2 ± 0.8	3.6 ± 0.9	18.1	1.4 ± 0.5	1.5 ± 0.4	13.5	1.0 ± 0.5	1.1 ± 0.3	4.6
200 - 499	3.3 ± 1.0	3.7 ± 0.9	19.1	1.7 ± 0.7	1.7 ± 0.4	6.6	1.0 ± 0.3	1.1 ± 0.4	15.2
p-value			0.940			0.563			0.445

Concentrations of analytes are presented as means ± SD. %Δ – percentage change; M0 – baseline; M12 – one year after treatment; p-value defines the level of significance when the percentage changes (%Δ) were compared (Unpaired t-test).

Table 8: Analysis of some factors associated with percentage changes in lipid (VLDL and LDL-C) concentrations

	VLDL			LDL-c			TC/HDL-c			LDL-c/HDL		
Variables	**M0**	**M12**	**%Δ**	**M0**	**M12**	**%Δ**	**M0**	**M12**	**%Δ**	**M0**	**M12**	**%Δ**
Sex												
Male	0.6 ± 0.2	0.7 ± 0.2	9.8	1.3 ± 0.5	1.5 ± 0.9	47.4	3.3 ± 1.2	3.8 ± 2.1	20.6	1.6 ± 1.1	1.9 ± 1.7	55.0
Female	0.7 ± 0.3	0.7 ± 0.2	3.8	1.4 ± 0.9	1.9 ± 0.8	31.9	3.4 ± 1.4	3.8 ± 1.7	19.9	1.6 ± 1.2	2.0 ± 1.3	45.8
p-value			0.574			0.788			0.965			0.321
CD_4(cells mm^{-3})												
<200	0.6 ± 0.2	0.7 ± 0.2	13.5	1.5 ± 0.6	1.9 ± 0.9	47.6	3.2 ± 1.0	3.9 ± 2.0	24.5	1.5 ± 0.8	2.2 ± 1.6	51.1
200 - 499	0.8 ± 0.3	0.7 ± 0.2	6.6	1.5 ± 0.9	1.8 ± 0.8	12.1	3.4 ± 1.4	3.7 ± 1.8	13.7	1.6 ± 1.2	1.9 ± 1.3	16.6
p-value			0.563			0.592			0.466			0.555

Concentrations of analytes are presented as means ± SD. %Δ – percentage change; M0 – baseline; M12 – one year after treatment; p-value defines the level of significance when the percentage changes (%Δ) were compared (Unpaired t-test).

Table 9: Comparison of percentage changes in lipid concentration in the various drug classes

	NVP		EFV		p-value			
Parameters	**CBV(%Δ)**	**d4T/3TC (%Δ)**	**CBV (%Δ)**	**d4T/3TC (%Δ)**	**p^a**	**p^b**	**p^c**	**p^d**
Lipid Profile (*mmol L-1*)								
TC	15.5	13.7	25.5	19.9	0.431	0.777	0.407	0.691
TG	3.4	6.3	5.2	7.9	0.884	0.742	0.937	0.914
HDL-c	17.8	7.8	11.5	38.4	0.738	0.462	0.731	0.364
VLDL	3.4	6.3	5.2	7.9	0.883	0.742	0.937	0.914
LDL-c	26.0	62.9	48.2	40.4	0.386	0.670	0.669	0.410
Atherogenic Index								
TC/HDL-c	6.3	9.9	26.7	39.8	0.178	0.259	0.323	0.379
LDL-c/HDL-c	22.9	56.9	44.4	27.8	0.428	0.890	0.744	0.613

%Δ-percentage change; p^a-defines the level of significance when NVP_{CBV} was compared with EFV_{CBV} (unpaired t-test); p^b-defines the level of significance when NVP_{CBV} was compared with $EFV_{d4T/3TC}$; p^c-defines the level of significance when $NVP_{d4T/3TC}$ was compared with EFV_{CBV}; p^d-defines the level of significance when $NVP_{d4T/3TC}$ was compared with $EFV_{d4T/CBV}$.

tween 200 – 499 cells mm^{-3} which was associated with increased percentage changes in TC and HDL-c (table 7 and 8).

Percentage changes in lipid & lipoprotein concentrations in various drug classes

A comparison of the percentage changes in lipid and lipoprotein concentrations in the various drug classes are shown in Table 9. No statistically significant differences were observed when percentage changes in lipid profile and atherogenic indices within the different drug classes were compared.

DISCUSSION

Initiation of an ART regimen containing NVP is associated with a 9.1% significant increase in weight compared to EFV treatment and this impact on patient weight is attributable to the NVP/CBV combination therapy. EFV treatment on the other hand was associated with significant increases in TC and LDL-c concentrations which is attributable to EFV/CBV combination therapy. Increases in HDL -c was observed in both treatment groups although not significant, but in the EFV group, the TC/ HDL-c and LDL-c/HDL-c ratios were increased compared to that in the NVP treatment group and this is as a result of the significant increases in TC and LDL-c elicited by EFV treatment. The absence of significant differences between NVP and EFV in this study is corroborated by the study of Nunez *et al.,* (2002) which found no significant differences between NVP and EFV.

HDL-c increase and NNRTI's

Data for ART-naïve patients starting therapy with NNRTI-based regimen are scarce but increases in HDL-c with the use of NVP or EFV have been described in studies for patients switching from a PI-based regimen to a NNRTI-based regimen (Martinez *et al.*, 1999; Negredo *et al.*, 2002). Results from this study showed increases in the mean baseline concentration of HDL-c in all four treatment categories at 24 months.

NVP and CBV combination therapy elicited an HDL-c increase of 0.21 mmol L^{-1}; NVP and d4T/3TC elicited a 0.09 mmol L^{-1} increase ; EFV

and CBV elicited a 0.10 mmol L^{-1} increase and with EFV and d4T/3TC treatment eliciting an HDL-c increase of 0.31 mmol L^{-1}. Tashima *et al.,* (2003) reported an HDL-c increase of 0.21 mmol L^{-1} in patients treated with EFV, zidovudine and 3TC with Fisac *et al.,* (2004) also reporting an HDL-c increase in treatment-naïve patients receiving NVP in combination with zidovudine/lamivudine nucleoside analogues. Negredo *et al.,* (2002) reported a 0.34 mmol L^{-1} increase in HDL-c concentration in treatment-naïve patients starting therapy with EFV, didanosine and d4T.

Studies have convincingly shown that increases in HDL-c concentration are associated with a significant decrease in mortality from coronary heart disease (CHD) which observation is independent from changes in LDL-c concentration (Manninen *et al.*, 1988; Rubins *et al.*, 1999). Other studies have also associated risk of cardiovascular disease (CVD) with low HDL-c concentrations (Assmann *et al.*, 1996; Robins, 2001). Extrapolations from such studies indicates that a 0.025 mmol L^{-1} HDL-c increase is associated with a 2 – 3% reduction in CHD risk, while a 1.0 mmol L^{-1} increase in LDL-c will increase CHD by 25%.

From this study, the mean absolute increases in HDL-c and LDL-c were 0.16 and 0.20 mmol L^{-1} respectively for patients on NVP and 0.16 and 0.70 mmol L^{-1} respectively for patients on EFV. Taking the observed effects on both HDL-c and LDL-c into account, an 11% reduction in CHD risk can be estimated for patients taking NVP compared to a 1.5% increase in CHD risk in patients taking EFV. The estimated 11% CHD reduction from this study compares well with a 15% CHD reduction risk estimated in patients taking NVP by van Leth *et al.,* (2004) while the 1.5% increase in CHD risk in patients taking EFV from this study represents increase in comparison to the 3% CHD risk reduction in patients taking EFV in the van Leth *et al.,* (2004) study.

A further analysis of the observed effects of HDL-c and LDL-c on CHD risk by the type of nucleoside-analogue being used with either NVP or EFV showed NVP + CBV reducing CHD risk by 5.8% with NVP + d4T /3TC, EFV + CBV and EFV + d4T/3TC increasing CHD risk by 14.8%, 6.3% and 117.7% respectively. It can therefore be deduced that NVP regimen (NVP + CBV) will lead to a lower atherogenicity index thereby leading to a better reduction in CHD risk compared to EFV regimen. Contrary to this finding, however, Ngondi *et al.,* (2007) in their study reported improvements in LDL-c/HDL-c and TC/HDL-c ratios when on d4T, 3TC and NVP combination therapy compared to EFV.

Changes in TG's and TC levels

Results of studies conducted by Molina *et al.,* (2000), Negredo *et al.,* (2002) and Fisac *et al.,* (2004) found that EFV causes a greater increase in TG levels than NVP regimen. This study did not show any significant differences in TG concentrations at baseline and one year after treatment with NVP or EFV. However, EFV regimen caused a 1.2% increase in TG concentration compared to NVP and this effect was further seen with the d4T/3TC nucleoside analogue component of EFV treatment. The d4T/3TC nucleoside analogue of NVP treatment also caused a 2.9% increase in TG concentration confirming reports of earlier studies which associated a gradual, progressive worsening of fat redistribution or lipodystrophy to d4T-containing ART regimen which eventually leads to increased TG and TC levels (Heath *et al.*, 2001; Dube *et al.*, 2002; Nolan *et al.*, 2003; Sattler, 2003; McComsey *et al.*, 2004).

A significant increase in TC levels was associated with EFV therapy compared to NVP therapy with EFV regimen causing a 9.5% increase in TC levels compared to NVP regimen. This finding is in agreement with the study of Martinez *et al.,* (1999) which reported elevations in cholesterol concentration with the use of EFV and that of Tashima *et al.,* (1999) which showed that with efavirenz-based regimen, TC and HDL-c tended to rise after 48 weeks of treatment. Contrary to reports of increases in TC levels being associated with d4T therapy (Mallal *et al.*, 2000), TC concentration increases observed in this study were associated with the CBV nucleoside

analogues of both EFV and NVP treatments other than d4T therapy.

The improvement in atherogenicity indices of patients on NVP compared to EFV therapy observed in this study correlated well with the findings of Ngondi *et al.,* (2007) and could be explained through the smaller increases in TC and LDL-c concentration in patients taking NVP compared to patients taking EFV.

CONCLUSION

The less atherogenic lipid profile of patients taking NVP in comparison to those taking EFV and the reduction in CHD risk associated with NVP + CBV combination therapy observed in this study should be factored into various considerations taken when selecting the most appropriate ART regimen for treatment naïve HIV-1 infected patients who are to be initiated on treatment. The added advantage will be the improvements in treatment adherence due to the flexibility associated with CBV co-formulation with respect to pill burden and this is of crucial importance for the sustained success of ART treatment considering the fact that the HIV-infected population requires other concomitant medications. Studies with matched controls should therefore be conducted to measure the rate of atherosclerosis development while controlling other known risk factors in Ghanaian HIV-1 infected patients.

COMPETING INTERESTS

The authors declare that they have no competing interests.

REFERENCES

Assmann G., Schulte H., von Eckardstein A. and Huang Y. (1996) High-density lipoprotein cholesterol as a predictor of coronary heart disease risk. The PROCAM experience and pathophysiological implications for reverse cholesterol transport. *Atherosclerosis* 124 SupplS11-20.

Bonnet F., Saves M., Droz C., Peuchant E., Chene G., Beylot J. and Morlat P. (2000) Increase of atherogenic plasma profile in HIV-infected patients treated with protease inhibitor-containing regimens. . *J. Acquir. Immune. Defic. Syndr* 25199-200.

Bozzette S.A., Ake C.F., Tam H.K., Chang S.W. and Louis T.A. (2003) Cardiovascular and cerebrovascular events in patients treated for humna immunodeficiency virus infection. *N Engl J Med* 348702-710.

Carr A. and Cooper D.A. (2000) Adverse effects of antiretroviral therapy. *Lancet* 356(9239), 1423-1430.

Carr A., Samaras K., Thorisdottir A., Kaufmann G.R., Chisholm D.J. and Cooper D.A. (1999) Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 353(9170), 2093-2099.

Cozzi-Lepri A., Phillips A.N., d'Arminio Monforte A., Piersantelli N., Orani A., Petrosillo N., Leoncini F., Scerbo A., Tundo P., Abrescia N. and Moroni M. (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(8), 1062-1069.

Dube M.P., Zackin R., Tebas P., Roubenoff R. and Mulligan K. (2002) Prospective study of regional body composition in antiretroviral-naive subjects randomized to receive zidovudine plus lamivudine or didanosine plus stavudine combined with nelfinavir, efavirenz, or both. A5005s, a substudy of ACTG 384. *Program and Abstracts of the 4th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV*, L18.

Fisac C., Fumero E., Crespo M., Roson B. and Virgili N. (2004) Metabolic changes in patiens switching from a protease inhibitor-containing regimen to abacavir (ABC), efavirenz (EFV), or nevirapine

(NVP): 24-Month results of randomised study. . *11th Conference on Retroviruses and Opportunistic Infection*, pp 105 - 105.

Flandre P., Peytavin G., Meiffredy V., Saidi Y., Descamps D. and Delagnes M. (2002) Adherence to antiretroviral therapy and outcomes in HIV-infected patients enrolled in an induction/maintenance randomized trial. *Antivir Ther* 7(2), 113-121.

Friedewald W.T., Levy R.I. and Fredrickson D.S. (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18(6), 499-502.

Heath K.V., Hogg R.S., Chan K.J., Harris M., Montessori V., O'Shaughnessy M.V. and Montanera J.S. (2001) Lipodystrophy-associated morphological, cholesterol and triglyceride abnormalities in a population-based HIV/AIDS treatment database. *AIDS* 15(2), 231-239.

Henry K., Melroe H., Huebsch J., Hermundson J., Levine C., Swensen L. and Daley J. (1998) Severe premature coronary artery disease with protease inhibitors. *Lancet* 351(9112), 1328.

Klein D. and Hurley L. (2003) Hospitalizations for coronary heart disease and myocardial infarction among men with HIV-1 infection: addtional follow-up. . *10th Conference on Retroviruses and Opportunistic Infections*, 747.

Mallal S.A., John M., Moore C.B., James I.R. and Mckinnon E.J. (2000) Contribution of serum triglycerides by the use of enzymes. *Clin. Chem.* 19476-482.

Mannheimer S., Friedland G., Matts J., Child C. and Chesney M. (2002) The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis* 34(8), 1115-1121.

Manninen V., Elo M.O., Frick M.H., Haapa K., Heinonen O.P., Heinsalmi P., Helo P., Huttunen J.K., Kaitaniemi P., Koskinen P. and et al. (1988) Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 260(5), 641-651.

Martinez E., Conget I., Lozano L., Casamitjana R. and Gatell J.M. (1999) Reversion of metabolic abnormalities after switching from HIV-1 protease inhibitors to nevirapine. *AIDS* 13(7), 805-810.

Matthews G.V., Sabin C.A., Mandalia S., Lampe F., Phillips A.N., Nelson M.R., Bower M., Johnson M.A. and Gazzard B.G. (2002) Virological suppression at 6 months is related to choice of initial regimen in antiretroviral-naive patients: a cohort study. *AIDS* 16(1), 53-61.

McComsey G.A., Ward D.J., Hessenthaler S.M., Sension M.G., Shalit P., Lonergan J.T., Fisher R.L., Williams V.C. and Hernandez J.E. (2004) Improvement in lipoatrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. *Clin Infect Dis* 38(2), 263-270.

Molina J.M., Ferchal F., Rancinan C., Raffi F., Rozenbaum W., Sereni D., Morlat P., Journot V., Decazes J.M. and Chene G. (2000) Once-daily combination therapy with emtricitabine, didanosine, and efavirenz in human immunodeficiency virus-infected patients. *J Infect Dis* 182(2), 599-602.

Negredo E., Cruz L., Paredes R., Ruiz L., Fumaz C.R., Bonjoch A., Gel S., Tuldra A., Balague M., Johnston S., Arno A., Jou A., Tural C., Sirera G., Romeu J. and Clotet B. (2002) Virological, immunological, and clinical impact of switching from protease inhibitors to nevirapine or to efavirenz in patients with human immunodeficiency virus infection and long-lasting viral suppression. *Clin Infect Dis* 34(4), 504-510.

Ngondi L.J., Etame S.H.L., Fonkoua M., Yangoua H. and Oben J. (2007) Lipid profile of infected patients treated with highly active antiretroviral therapy in cameroon. *J. Med. Sci.* 7670-673.

Nolan D., Hammond E., James I., McKinnon E. and Mallal S. (2003) Contribution of nucleoside-analogue reverse transcriptase inhibitor therapy to lipoatrophy from the population to the cellular level. *Antivir Ther* 8(6), 617-626.

Nunez M., Soriano V., Martin-Carbonero L., Barrios A., Barreiro P., Blanco F., Garcia-Benayas T. and Gonzalez-Lahoz J. (2002) SENC (Spanish efavirenz vs. nevirapine comparison) trial: a randomized, open-label study in HIV-infected naive individuals. *HIV Clin Trials* 3(3), 186-194.

Palella F.J., Jr., Delaney K.M., Moorman A.C., Loveless M.O., Fuhrer J., Satten G.A., Aschman D.J. and Holmberg S.D. (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 338(13), 853-860.

Podzamczer D., Ferrer E., Consiglio E., Gatell J.M., Perez P., Perez J.L., Luna E., Gonzalez A., Pedrol E., Lozano L., Ocana I., Llibre J.M., Casiro A., Aranda M., Barrufet P., Martinez -Lacasa J., Miro J.M., Badia X., Casado A., Lupo S., Cahn P., Manos M. and Estela J. (2002) A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the Combine Study). *Antivir Ther* 7(2), 81-90.

Robins S.J. (2001) Targeting low high-density lipoprotein cholesterol for therapy: lessons from the Veterans Affairs High-density Lipoprotein Intervention Trial. *Am J Cardiol* 88 (12A), 19N-23N.

Rubins H.B., Robins S.J., Collins D., Fye C.L., Anderson J.W., Elam M.B., Faas F.H., Linares E., Schaefer E.J., Schectman G., Wilt T.J. and Wittes J. (1999) Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. *N Engl J Med* 341(6), 410-418.

Sattler F. (2003) Body habitus changes related to lipodystrophy. *Clin Infect Dis* 36(Suppl 2), S84-90.

Staszewski S., Morales-Ramirez J., Tashima K.T., Rachlis A., Skiest D., Stanford J., Stryker R., Johnson P., Labriola D.F., Farina D., Manion D.J. and Ruiz N.M. (1999) Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med* 341(25), 1865-1873.

Stebbing J., Gazzard B. and Douek D.C. (2004) Where does HIV live? *N Engl J Med* 350 (18), 1872-1880.

Tashima K., Staszewski S. and Stryker R. (1999) A phase III, multicenter, randomized, open-label study to compare the antiretroviral activity and tolerability of efavirenz + indinavir, versus efavirenz + zidovudine + lamivudine, versus indinavir + zidovudine + lamivudine at 48 weeks. . In *6th Conference on Retroviruses and Opportunistic Infections*. Chicago, IL.

Tashima K.T., Bausserman L., Alt E.N., Aznar E. and Flanigan T.P. (2003) Lipid changes in patients initiating efavirenz- and indinavir-based antiretroviral regimens. *HIV Clin Trials* 4(1), 29-36.

van der Valk M., Kastelein J.J., Murphy R.L., van Leth F., Katlama C., Horban A., Glesby M., Behrens G., Clotet B., Stellato R.K., Molhuizen H.O. and Reiss P. (2001) Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an antiatherogenic lipid profile. *AIDS* 15(18), 2407-2414.

van Leth F., Phanuphak P., Ruxrungtham K., Baraldi E., Miller S., Gazzard B., Cahn P., Lalloo U.G., van der Westhuizen I.P., Malan D.R., Johnson M.A., Santos B.R., Mulcahy F., Wood R., Levi G.C., Reboredo G., Squires K., Cassetti I., Petit D., Raffi F., Katlama C., Murphy R.L., Horban A., Dam J.P., Hassink E., van Leeuwen R., Robinson P., Wit F.W. and Lange J.M. (2004) Comparison of first-line antiretroviral therapy with

regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 363(9417), 1253-1263.

ISSN 2026-6294