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

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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 increase in TC/HDL-c and LDL-c/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.

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 revolutionized 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;
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 counseling 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°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 CD4 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 CD4 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:

\[
\text{Percent change} = \frac{\text{Concentration at month 12} - \text{Concentration at month 0}}{\text{Concentration at month 0}} \times 100
\]

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 characteristics 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

| Parameters          | 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      |       |       |         |
| CD4 (cells mm⁻³)    | 259.3±136.9 | 231.3±149.8 | 267.9±133.1   |       |       |         |
| pCD4 classification | <200        | 18(29.5)    | 6(40.0)       |       |       |         |
|                    | 200 - 499   | 39(63.9)    | 8(53.3)       |       |       |         |
|                    | >500        | 4(6.6)      | 0(0.0)        |       |       |         |
| Lipid Profile (mmolL⁻¹) |          |             |               |       |       |         |
| TC                  | 3.2±1.0     | 3.0±0.6     | 3.3±1.0       |       |       |         |
| TG                  | 1.6±0.7     | 1.5±0.4     | 1.6±0.7       |       |       |         |
| HDL-c               | 1.0±0.4     | 0.9±0.3     | 1.1±0.4       |       |       |         |
| VLDL                | 0.7±0.3     | 0.6±0.2     | 0.7±0.3       |       |       |         |
| LDL-c               | 1.4±0.8     | 1.3±0.5     | 1.4±0.9       |       |       |         |
| Atherogenic Index   |             |             |               |       |       |         |
| TC/HDL              | 3.4±1.3     | 3.3±1.2     | 3.4±1.4       |       |       |         |
| LDL-c/HDL           | 1.6±1.1     | 1.6±1.1     | 1.6±1.2       |       |       |         |

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.

Parameter changes when stratified by NNR-RTI use:

- Treatment with HAART significantly reduced the mean total cholesterol (TC) and triglycerides (TG) concentrations in the study participants at baseline (3.2±1.0 mmolL⁻¹ and 1.4±0.7 mmolL⁻¹, respectively) (p = 0.009) and at month 12 (3.5±0.8 mmolL⁻¹ and 1.2±0.7 mmolL⁻¹, respectively) (p = 0.009). The reduction in mean total cholesterol was statistically significant both in males (3.0±0.8 mmolL⁻¹ and 1.4±0.7 mmolL⁻¹, respectively) (p = 0.009) and in the female patients (3.4±0.9 mmolL⁻¹ and 1.2±0.8 mmolL⁻¹, respectively) (p = 0.009). The reduction in mean triglycerides was statistically significant both in males (1.4±0.7 mmolL⁻¹ and 1.2±0.8 mmolL⁻¹, respectively) (p = 0.009) and in the female patients (1.3±0.8 mmolL⁻¹ and 1.1±0.8 mmolL⁻¹, respectively) (p = 0.009).

- The atherogenic index (TC/HDL) also showed a significant decrease in the study participants at baseline (3.2±1.0 mmolL⁻¹) and at month 12 (3.5±0.8 mmolL⁻¹), and at month 12 (3.5±0.8 mmolL⁻¹) (p = 0.009) was statistically significant.
### Table 2: Characteristics of the nevirapine group stratified by specific NRTI backbone

| Parameters       | Total (n = 27) | CBV (n = 16) | d4T/3TC (n = 11) |
|------------------|----------------|--------------|------------------|
|                  | 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       | 48.7±3.3     | 0.006            | 48.5±5.9       | 51.7±9.8     | 0.353            |
| CD4 (cells mm⁻³) | 270.8±115.0    | 280.2±130.3  | 0.542            | 257.1±92.8     | 281.1±116.9  | 0.599            |

CD4 classes

| CD4 classes | Total (n = 34) | CBV (n = 26) | d4T/3TC (n = 8) |
|-------------|----------------|--------------|-----------------|
|             | Month 0        | Month 12     | p value          | 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       | 51.1±10.3    | 0.006            | 49.9±7.1       | 49.3±9.6     | 0.885            |
| CD4 (cells mm⁻³) | 250.3±153.2 | 265.6±154.8  | 0.974            | 200.5±146.0    | 233.3±108.9  | 0.619            |

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.

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

| Parameters       | Total (n = 34) | CBV (n = 26) | d4T/3TC (n = 8) |
|------------------|----------------|--------------|-----------------|
|                  | Month 0        | Month 12     | p value          | 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       | 51.1±10.3    | 0.006            | 49.9±7.1       | 49.3±9.6     | 0.885            |
| CD4 (cells mm⁻³) | 250.3±153.2    | 265.6±154.8  | 0.974            | 200.5±146.0    | 233.3±108.9  | 0.619            |

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 CD4 counts and the distribution of patients by CD4 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; %Δ = 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 ± 1.0 mmol L\(^{-1}\) (p = 0.006; %Δ = 35.1) while that of patients on NVP showed no significant change (p = 0.704). Of the two drug classes, EFV increased the LDL-c concentration by 39.3% compared to NVP but a comparison of the percentage changes within the NVP (n = 27) and EFV (n = 34) groups after one year of treatment showed no statistically significant differences.

### Table 4: Percentage change in lipid concentrations, weight and CD4 in the study group stratified by NNRTI use

| Parameters | NVP (n = 27) | EFV (n = 34) | Difference in %Δ (NVP-EVF) | 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 | 0.534 |
| 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 |
| CD4 (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 shown 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

| Parameters            | CBV (16) | Month 0 | %Δ | p-value of %Δ | Month 12 | %Δ | p-value of %Δ | Difference in %Δ | p-value of %Δ |
|-----------------------|----------|---------|----|----------------|----------|----|----------------|------------------|----------------|
| Lipid Profile (mmol L⁻¹) |          |         |    |                |          |    |                |                  |                |
| TC                    |          | 3.7 ± 1.0 | 40 ± 1.0 | 3.3 ± 0.6 | 3.6 ± 0.9 | 13.7 | 0.3 | 0.18           | 0.422           |
| TG                    |          | 1.7 ± 0.6 | 1.7 ± 0.4 | 0.7 ± 0.4 | 1.7 ± 0.5 | 6.3 | 0.097 | 0.83           | 0.3            |
| HDL-c                 |          | 1.2 ± 0.4 | 0.7 ± 0.4 | 0.5 ± 0.4 | 1.2 ± 0.5 | 7.8 | 0.027 | 0.5            | 1             |
| VLDL                  |          | 0.7 ± 0.3 | 0.7 ± 0.3 | 0.5 ± 0.3 | 0.8 ± 0.3 | 6.3 | 0.092 | 0.83           | 0.3            |
| LDL-c                 |          | 1.7 ± 0.0 | 1.7 ± 0.0 | 1.4 ± 0.0 | 1.7 ± 0.0 | 0.3 | 0.382 | 0.372          | 0.3            |
| Atherogenic Index     |          | 3.2 ± 1.3 | 3.2 ± 1.0 | 2.9 ± 0.6 | 3.2 ± 0.9 | 9.9 | 0.027 | 0.817          | 0.3             |

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

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.

HIV therapeutic agents on lipid profile among HIV patients

Quaye et al.,
In the EFV group, CBV elicited a 25.5% significant increase in LDL-cholesterol 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-cholesterol 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 increased TC/HDL-cholesterol ratio by 4.3% and LDL/HDL-cholesterol 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 CD4 counts on lipid and lipoprotein concentration

An analysis of the association of sex and CD4 counts with changes in lipid (TC, TG, HDL-cholesterol, VLDL, and LDL-cholesterol) concentrations and atherogenic indices (TC/HDL and LDL-cholesterol/HDL-cholesterol) are presented in Tables 7 and 8. The percentage changes in TC and HDL-cholesterol concentrations however showed no statistically significant differences when compared.

CD4 counts of <200 cells mm^-3 was associated with increased percentage changes in TC, VLDL, LDL-cholesterol concentrations and the atherogenic indices defined by TC/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol in comparison to CD4 counts of 100-200 cells mm^-3 and >300 cells mm^-3. Likewise, the percentage changes in TC and HDL-cholesterol concentrations however showed no statistically significant differences when compared.

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 |
|---------------------|----------|-------------|------------------|---------------|
| **Lipid Profile (mmol L^-1)** |          |             |                  |               |
| TC                  | 2.9 ± 1.0| 3.5 ± 0.8   | 25.5             | 0.046         |
| TC                  | 3.0 ± 0.8| 3.4 ± 0.4   | 19.9             | 0.173         |
| TG                  | 1.6 ± 0.8| 1.6 ± 0.4   | 5.2              | 0.525         |
| TG                  | 1.5 ± 0.6| 1.6 ± 0.5   | 7.9              | 0.832         |
| HDL-cholesterol     | 0.9 ± 0.4| 1.0 ± 0.4   | 11.5             | 0.930         |
| HDL-cholesterol     | 0.8 ± 0.4| 0.9 ± 0.4   | 38.4             | 0.890         |
| VLDL                | 0.7 ± 0.4| 0.7 ± 0.2   | 5.2              | 0.525         |
| VLDL                | 0.7 ± 0.3| 0.7 ± 0.2   | 7.9              | 0.832         |
| LDL-cholesterol     | 1.2 ± 0.8| 1.8 ± 0.7   | 48.2             | 0.013         |
| LDL-cholesterol     | 1.4 ± 0.6| 1.8 ± 0.7   | 40.4             | 0.256         |
| **Atherogenic Index** |          |             |                  |               |
| TC/HDL-cholesterol  | 3.5 ± 1.5| 4.1 ± 2.3   | 26.7             | 0.207         |
| TC/HDL-cholesterol  | 4.0 ± 1.6| 4.6 ± 2.0   | 22.4             | 0.490         |
| LDL-cholesterol/HDL-cholesterol | 1.8 ± 1.3| 2.2 ± 1.6 | 44.4            | 0.106         |
| LDL-cholesterol/HDL-cholesterol | 2.1 ± 1.3| 2.6 ± 1.6 | 27.8            | 0.473         |

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.

In the EFV group, CBV elicited a 25.5% significant increase in TC concentration and a 48.2% significant increase in LDL-cholesterol concentration when compared to d4T/3TC combination therapy.
Table 7: Analysis of some factors associated with percentage changes in lipid (TC, TG and HDL-C) concentrations

| Variables | TC 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 |     |
| CD4 (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

| Variables | VLDL M0 | M12 | %Δ | LDL-c M0 | M12 | %Δ | TC/HDL-c M0 | M12 | %Δ | LDL-c/HDL 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 |     |     |    |     |     |
| CD4 (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).
between 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
HIV therapeutic agents on lipid profile among HIV patients

Quaye et al.,

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-naive 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-naive 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
analogue 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.

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