Carotid intima-media thickness, flow-mediated dilatation and proteinuria in patients of human immunodeficiency virus-positive patients: A case–control study

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Abstract

Introduction: Endothelium-dysfunction (ED) is a surrogate marker of coronary atherosclerotic disease. Carotid intima-media thickness (CIMT), flow-mediated dilatation (FMD), and proteinuria are surrogate markers of ED. Few studies have shown that patients with HIV have impaired endothelial function and are thus at risk of accelerated atherosclerosis. Materials and Methods: The present study assessed ED in HIV patients by various biophysical parameters as brachial artery FMD, CIMT, and proteinuria. A total of 43 HIV-infected patients were compared with 25 healthy controls who were healthy. Results: Mean age of patients with HIV was 33.84 ± 5.61 years while that of healthy controls was 31.48 ± 5.40 years. Male to female ratio among cases was 24:19 while among controls was 17:8. Mean CIMT was significantly higher among cases than control (0.513 ± 0.079, 0.452 ± 0.050 mm, respectively, \( P = 0.001 \)). Percentage change in FMD was significantly lower among cases than control (3.27 ± 2.01, 6.96 ± 1.28, respectively, \( P = 0.001 \)). Urine protein grading was significantly different between cases and controls (\( P = 0.007 \)), with stable HIV cases having significantly higher urine protein grading compared to healthy controls. However, no correlation was seen between CIMT, FMD, and proteinuria overall among cases and controls. Conclusions: HIV-infected patients have significant impairment of endothelial function, in the form of increased CIMT, impaired FMD, and more proteinuria as compared to healthy controls.

Keywords: Carotid intima-media thickness, endothelial dysfunction, flow-mediated dilatation, HIV, subclinical atherosclerosis

Introduction

HIV-infected patients are at higher risk for cardiovascular events.¹ Thus, we need to identify the patients at risk at the earliest using easily obtainable, noninvasive, and inexpensive markers. Endothelial dysfunction (ED) is an early step that leads to progression of atherosclerosis. Proteinuria is another marker which predicts future cardiovascular events.²

The development of systemic ED has been suggested as the link between the presence of proteinuria and development of cardiovascular disease.³ Not only HIV, its therapies have also been associated with ED.⁴ Endothelial function can be assessed by flow-mediated dilatation (FMD).⁵ Carotid intima-media thickness (CIMT) is a measure of the extent of early arterial wall changes. Increased carotid IMT is a strong predictor of acute coronary events.⁶ Thus, we conducted a study to look at the endothelial cell dysfunction in stable HIV patients and compare with healthy controls.

Materials and Methods

The study population included forty-three consecutive stable HIV patients attending Medical OPD and HIV clinic at a tertiary care hospital at New Delhi.

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The aims of our study were:
1. To study endothelial cell dysfunction in stable HIV patients as a marker of premature atherosclerosis by FMD, proteinuria, and carotid intima-media thickness
2. To study its correlation with healthy controls.

We included stable patients of HIV (confirmed by IGM ELISA). Patients with age <18 years and >40 years, overweight (body mass index >25 kg/m²), suffering from preexisting diabetes mellitus or hypertension, receiving highly active antiretroviral therapy, suffering from known renal disease (serum creatinine >1.4 mg/dl or >124 µmol/L), history of cardiovascular and ischemic heart disease, fever (temperature >38.0°C) currently or 2 days before enrolment in the study, suffering from any opportunistic infection, smokers, alcoholics, or other active substance abuse, on drugs such as growth hormone, systemic steroids, ketoconazole, any form of estrogen, progesterone, testosterone, or any anabolic agents within 3 months before enrolment in the study and pregnant women were excluded from the study.

Twenty-five apparently healthy controls were residents and nurses working in the same tertiary care hospital. Exclusion criteria for controls were same as that for the HIV cases.

All the patients and controls in the study group were subjected to detailed history and physical examination. Informed consent was taken from both cases as well as controls. The study protocol has been evaluated and approved by the hospital Ethical Committee.

Following investigations were carried out in all the patients and controls:
1. Brachial FMD using 10MHz linear array transducer
2. Common Carotid Ultrasonography—Using 7.5MHZ B-mode ultrasound with high-density lipoprotein 3500 machine, (ATL, USA) equipped with color flow imaging and pulse Doppler and one examiner examined the result of all the patients
3. Urine examination—single spot urine sample for proteinuria and cells/casts was obtained.

Statistical analysis
The data of all patients were entered into Microsoft Excel version 2007. The data analysis was done by the SPSS software for window version 17 (IBM Corporation, New York, United States). Quantitative variables were reported as mean ± standard deviation and were compared by Student’s t-test or Mann–Whitney test as appropriate. One-way analysis of variance (ANOVA) model was used to compare cases and controls for difference of urine protein grading. Qualitative variables were reported and compared by Chi-square test or Fisher’s exact test as appropriate. $P < 0.05$ was considered statistically significant. Continuous variables were correlated using Pearson’s correlation coefficient.

Results
Our study included 43 cases and 25 healthy controls. Proteinuria was estimated by dip stick method which is represented in Table 1. Baseline characteristics of both cases and controls are shown in Table 2.

The studied parameters were compared which is shown in Table 3.

Urine protein was also compared among cases and controls which is shown in Table 4.

Urine protein grading was significantly different between cases and controls ($P = 0.007$), with stable HIV cases having significantly higher urine protein grading compared to healthy controls.

Table 1: Dipstick proteinuria ranges

| Dipstick grading | Semi-quantitative urine protein (mg/dl) |
|------------------|----------------------------------------|
| Negative/nil     | 0                                      |
| Trace            | 15-30                                   |
| 1+               | 30-100                                  |
| 2+               | 100-300                                 |
| 3+               | 300-1000                                |
| 4+               | >1000                                   |

Table 2: Baseline characteristics of cases and controls

| Characteristics          | Cases (n=43) | Controls (n=25) |
|--------------------------|--------------|-----------------|
| Age (years)              | 33.8±±5.61   | 31.48±±5.40     |
| Sex (male:female)        | 24:19        | 17:8            |
| BMI (kg/m²)              | 20.67±2.63   | 21.52±1.16      |
| ESR (mm at 1 h)          | 9.47±2.62    | 11.56±1.87      |
| Hemoglobin level (g/dl)  | 12.46±1.18   | 13.51±0.45      |
| Fasting blood sugar (mg/dl) | 80.0±±8.18   | 80.28±5.42      |
| Blood urea (mg/dl)       | 23.3±±5.32   | 23.48±2.61      |
| Serum creatinine (mg/dl) | 0.62±±0.25   | 0.32±±0.11      |
| Serum uric acid (mg/dl)  | 5.10±±0.99   | 3.62±±0.57      |
| Total cholesterol (mg/dl) | 141.16±28.53 | 130.12±15.23   |
| Serum triglyceride (mg/dl) | 124.35±33.79 | 118.76±16.21   |
| LDL cholesterol (mg/dl)  | 89.58±20.93  | 110.68±18.42   |
| HDL cholesterol (mg/dl)  | 43.26±7.66   | 52.84±4.07      |
| VLDL cholesterol (mg/dl) | 29.7±±4.25   | 25.68±4.03      |

Table 3: Comparison of studied parameters between cases and controls

| Parameters          | Patients (n=43) | Controls (n=25) | $P$   |
|---------------------|-----------------|-----------------|-------|
| CIMT right (mm)     | 0.516±0.084     | 0.452±0.050     | 0.001 |
| CIMT left (mm)      | 0.510±0.095     | 0.452±0.050     | 0.006 |
| CIMT mean (mm)      | 0.513±0.079     | 0.452±0.050     | 0.001 |
| Brachial artery diameter at rest (cm) | 0.379±0.037 | 0.345±0.039  | <0.001 |
| Peak brachial artery diameter on hyperemia (cm) | 0.392±0.040 | 0.366±0.042  | 0.02  |
| Percent FMD         | 3.27±2.01       | 6.96±1.28       | <0.001 |

CIMT: Carotid intima media thickness; FMD: Flow-mediated dilatation
controls (one-way ANOVA). In urine microscopy, cells and casts were absent both in cases and controls.

The association between the parameters was calculated which is shown in Table 5.

**Discussion**

In this study, we studied forty-three stable HIV patients and twenty-five apparently healthy controls and looked for any significant difference between stable HIV patients and controls with respect to CIMT, FMD, and proteinuria and examined the relationship between CIMT, FMD, and proteinuria and their use as a marker of ED for premature atherosclerosis.

In our study, we found higher baseline mean CIMT in HIV-positive patients (0.513 ± 0.079 mm), as compared to controls (0.452 ± 0.050 mm) with a significant difference (P = 0.001). Table 6 summarizes previous major studies on CIMT in HIV patients.

In our study, we excluded the patients on HAART to prevent its effect on CIMT.

We also found that in stable HIV patients have increased in brachial artery diameter in response to passive hyperemia

### Table 4: Comparison of urine protein grading between cases and controls

| Urine protein grading | Total |
|-----------------------|-------|
| Nil                   | 19    |
| 1+                    | 8     |
| 2+                    | 13    |
| 3+                    | 3     |
| Controls              | 21    |
| 1+                    | 3     |
| 2+                    | 1     |
| 3+                    | 0     |
| Total                 | 40    |
| 1+                    | 11    |
| 2+                    | 14    |
| 3+                    | 3     |
| 68                    |       |

### Table 5: Association between various studied parameters overall in cases and controls

| Parameters (both cases and controls) | Association | Level of significance (P) |
|--------------------------------------|-------------|---------------------------|
| CIMT versus percentage FMD           | Not significantly | 0.107                     |
| CIMT versus urine protein grading    | Not significantly | 0.764                     |
| Percentage FMD versus urine protein grading | Not significantly | 0.177                     |

CIMT: Carotid intima media thickness; FMD: Flow-mediated dilatation

### Table 6: Summary of previous major studies on carotid intima media thickness in human immunodeficiency virus patients

| Authors                  | Patients (n) | Results                                                                 |
|--------------------------|--------------|-------------------------------------------------------------------------|
| Kaplan et al[17]         | 1931 cases   | CIMT was not significantly different in HIV-infected versus uninfected patients after adjustment for metabolic risk factors |
| Lorenz et al[18]         | 292 cases    | CIMT was higher in HIV infected compared to uninfected patients (absolute difference 0.044 mm, 95% CI 0.021-0.066 mm, P=0.0001) Use of HAART had an independent effect on CIMT |
| Currier et al[19]        | 89 cases     | CIMT progression at 3 years was not significantly different between PI treated and non-PI treated patients and between HIV infected and matched uninfected controls |
| de Saint Martin et al[20] | 154 cases   | CIMT predictors included age, SBP, and triglyceride value (<0.001, <0.001 and 0.02 respectively). Duration of PI, especially that of lopinavir, was also correlated with CIMT after adjustment (P=0.01) |
| Hsue et al[21]           | 93 cases     | CIMT was higher in HIV infected versus uninfected patients (0.95 vs. 0.68 mm, P<0.001) |
| Jericó et al[22]         | 132 cases    | CIMT >0.8 mm or presence of plaque was found in 41.7% of patients. Risk of carotid atherosclerosis was increased in patients on HAART compared to treatment naive patients (OR 10.5, 95% CI 2.8-39) |
| Maggi et al[23]          | 133 cases    | PI use appeared associated with a more rapid onset of carotid lesions compared to patients treated with NNRTIs, with more rapid evolution of previous lesions |
| Mangli et al[24]         | 327 cases    | CIMT did not differ by HAART regimen For men age and waist circumference predicted common CIMT, for women, age and BMI were predictors |
| Currier et al[25]        | 89 cases     | CIMT was not significantly different in HIV-infected patients on PI treatment for >2 years compared with those without prior PI use or uninfected controls (0.690 vs. 0.712 vs. 0.698 mm) |
| Hsue et al[26]           | 143 cases    | CIMT progression at 1 year was higher in HIV infected versus uninfected patients (0.074±0.13 mm vs. 0.006±0.05 mm, P=0.002). Predictors of progression included age, latino race, and nadir CD4 count ≤200 |
| Depairon et al[27]       | 168 cases    | HIV infected patients had more carotid or femoral plaques when compared with uninfected patients (61% vs. 46%, P=0.03). Independent predictors of plaque included age, male gender, LDL cholesterol, and smoking. PI use was not associated with the presence of plaque |
| Maggi et al[28]          | 102 cases    | Carotid plaque was higher than expected in patients receiving PI therapy, when compared with those without PI use and noninfected controls (52.7% vs. 14.9% vs. 6.7%) |

CIMT: Carotid intima media thickness; HIV: Human immunodeficiency virus; CI: Confidence interval; HAART: Highly active antiretroviral therapy; PI: Protease inhibitor; SBP: Systolic blood pressure; OR: Odds ratio; NNRTIs: Nonnucleoside reverse transcriptase inhibitor; BMI: Body mass index; LDL: Low-density lipoprotein
which was significantly lower as compared to healthy controls (3.27 ± 2.01 mm vs. 6.96 ± 1.28 mm, P < 0.001). Furthermore, significantly lower HIV cases had percent FMD ≥4.5% as compared to controls (23.3% vs. 100%, P < 0.001). Table 7 summarizes previous major studies of FMD in HIV patients.

Our finding of unequal percentage FMD in HIV patients and non-HIV participants is in agreement with previous studies that found decreased FMD in HIV patients compared to HIV-uninfected controls in but in contrast to other studies that found equal FMD in HIV patients and non-HIV participants. Various explanations have been proposed for conflicting results regarding brachial FMD in the literature. These include heterogeneity in patient populations being studied, different measurement protocols or inadequate sample sizes.

We also found significant difference in urine protein grading between stable HIV cases and healthy controls, with overall urine protein grading significantly higher in HIV cases compared to healthy controls (P = 0.007). Table 8 summarizes the previous major studies on proteinuria in HIV patients.

The high prevalence of proteinuria in this cohort of HIV-infected patients in our study is similar to earlier reports from HIV-infected children and adults. The implication of this observation is that markers of kidney damage such as proteinuria should be searched for in HIV-infected patients with advanced clinical and or immunological stage of HIV disease.

We also found a weak inverse relationship between carotid IMT and brachial percent FMD but not significant (r = −0.197, P = 0.107), when data were combined both for HIV cases and healthy controls. There is only one previous study by Oduyeungbo et al. (257 HIV patients), that has validated this correlation in HIV patients with borderline significance (r = −0.126, P = 0.043).

We did not find any significant correlation between percentage FMD and proteinuria, overall in HIV cases and healthy controls (P = 0.177). After an extensive review of literature, we could find only one pilot study of its kind to study the relation between FMD and proteinuria in stable HIV patients. This study by Gupta et al. (34) of 34 stable HIV patients (28 nonproteinuric and 6 proteinuric), also could not establish any significant correlation between proteinuria and FMD.

We did not find any significant correlation between CIMT and proteinuria (P = 0.764), overall in HIV cases and healthy controls and also, separately for HIV cases (P = 0.178). To the best of our knowledge, this is the first study of its kind to study the association between CIMT and proteinuria.

Although HIV infection appears to be associated with substantial impairment of endothelial function, the degree to which this impairment translates into increased risk for cardiovascular disease in persons with HIV infection is still largely unknown.

Large prospective, well-controlled studies are required to demonstrate that impaired endothelial functions translate into increased cardiovascular events and premature death in stable HIV patients.

Several limitations of our study need attention. First, the sample size of our study was small, limiting our ability to detect potentially clinically important associations. Second, proteinuria was determined by a semi-quantitative measure of urine protein concentration (dipstick), which is inferior to quantitative measures such as protein-to-creatinine ratio from a random or 24-h sample. Third, other potential confounders that were not accounted for include diet, physical activity, duration of HIV infection, and CD4 count.

| Authors          | Patients (n) | Results                                                                 |
|------------------|--------------|-------------------------------------------------------------------------|
| Blanco et al.    | 28 patients  | Treated HIV patients had significantly lower percentage FMD (5.93±3.56) than healthy controls (10.64±3.08, P=0.008). Naive patients had an intermediate FMD but this was not statistically significant |
| Nolan et al.     | 24 patients  | FMD was not significantly different between HIV patients and controls    |
| Stein et al.     | 37 patients  | Use of PIs in HIV is associated with atherosgenic lipoprotein changes and impaired FMD                                |
| van Wijk et al.  | 37 HIV patients | The FMD was impaired in HIV-infected patients without the MS and the diabetic patients (5.1%±0.4% and 4.9%±0.6%, respectively) compared with controls (8.8%±0.7%). The HIV-infected patients with the MS had even more impaired FMD (2.5%±0.3%) |

| Authors          | Patients (n) | Results                                                                 |
|------------------|--------------|-------------------------------------------------------------------------|
| Chaparro et al.  | 286 HIV children | The occurrence of proteinuria was 33% overall, with 11% having nephrotic range proteinuria |
| Szczecz et al.   | 2059 HIV women | 32% had proteinuria on initial evaluation |
| Esezobor et al.  | 88 HIV children | 20.5% of HIV-infected children had proteinuria, compared with 6% of the 50 controls, with significant difference (P=0.026) |
| Eke et al.       | 250 HIV children | 18.8% prevalence of proteinuria |
| Emem et al.      | 400 HIV patients | Dipstick positive proteinuria was 1+ in 82 (20.5%) patients, 2+ in 39 (9.8%), 3+ in 17 (4.3%), and 4+ in 14 (3.5%) patients |
| Agaba et al.     | 79 HIV patients | 20 (25.3%) HIV patients had proteinuria compared to 7 (12.2%) of controls, which was significantly different. The mean protein excretion/24 h was significantly higher in the AIDS group compared to controls, (2.99±0.54 g and 0.56±0.12 g respectively, P=0.001) |
Conclusions

Indian stable HIV patients have increased ED, as evidenced by increased carotid intima-media thickness, impaired FMD, and higher proteinuria. This subclinical ED would probably translate into premature atherogenesis and increased vascular events in these patients. However, the correlation between these various surrogates of endothelial cell function was poor in Indian stable HIV patients.

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Conflicts of interest
There are no conflicts of interest.

References

1. James JS. Atherosclerosis risk increased with HIV; Treatment effects unclear. AIDS Treat News 2004;26:4-5.
2. Currie G, Delles C. Proteinuria and its relation to cardiovascular disease. Int J Nephrol Renovasc Dis 2013;7:13-24.
3. Solages A, Vita JA, Thornton DJ, Murray J, Heeren T, Craven DE, et al. Endothelial function in HIV-infected persons. Clin Infect Dis 2006;42:1325-32.
4. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D; Clinical Epidemiology Group from the French Hospital Database, et al. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS 2003;17:2479-86.
5. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: A consensus statement from the American Society of Echocardiography Carotid Intima-media Thickness Task Force. Endorsed by the society for vascular medicine. J Am Soc Echocardiogr 2008;21:93-111.
6. George JM, Bhat R, Pai KM, S A, Jeganathan J. The carotid intima media thickness: A predictor of the clinical coronary events. J Clin Diag Res 2013;7:1082-5.
7. Kaplan RC, Kingsley CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Low CD4+ T-cell count as a major atherosclerosis risk factor in HIV-infected women and men. AIDS 2008;22:1615-24.
8. Lorenz MW, Stephan C, Harmjanz A, Staszewski S, Buehler A, Bickel M, et al. Both long-term HIV infection and highly active antiretroviral therapy are independent risk factors for early carotid atherosclerosis. Atherosclerosis 2008;196:720-6.
9. Currier JS, Kendall MA, Henry WK, Alston-Smith B, Torriani FJ, Tebas P, et al. Progression of carotid artery intima-media thickness in HIV-positive children and cumulative time of exposure to antiretroviral therapy (SHIVA study). Atherosclerosis 2006;185:361-7.
10. de Saint Martin L, Vandhuicq O, Guillou P, Bellein V, Bressollette L, Roudaut N, et al. Premature atherosclerosis in HIV positive patients and cumulated time of exposure to antiretroviral therapy (SHIVA study). Atherosclerosis 2006;185:361-7.
11. Hsue PY, Hunt PW, Sinclair E, Bredt B, Franklin A, Killian M, et al. Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses. AIDS 2006;20:2275-83.
12. Jericó C, Knobel H, Calvo N, Sorli ML, Guelar A, Gimeno-Bayón JL, et al. Subclinical carotid atherosclerosis in HIV-infected patients: Role of combination antiretroviral therapy. Stroke 2006;37:812-7.
13. Maggi P, Perilli F, Lillo A, Gargiulo M, Ferraro S, Grisorio B, et al. Rapid progression of carotid lesions in HAART-treated HIV-1 patients. Atherosclerosis 2007;192:407-12.
14. Mangili A, Gerrior J, Tang AM, O’Leary DH, Polak JK, Schaefer EJ, et al. Risk of cardiovascular disease in a cohort of HIV-infected adults: A study using carotid intima-media thickness and coronary artery calcium score. Clin Infect Dis 2006;43:1482-9.
15. Currier JS, Kendall MA, Zackin R, Henry WK, Alston-Smith B, Torriani FJ, et al. Premature atherosclerosis in HIV-infected individuals – Focus on protease inhibitor therapy. AIDS 2001;15:329-34.
16. Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, et al. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. Circulation 2004;109:1603-8.
17. Depaireon M, Chessex S, Sudre P, Rodondi N, Doser N, Chave JP, et al. Premature atherosclerosis in HIV-infected patients with low or mild cardiovascular risk. J Antimicrob Chemother 2006;58:133-9.
18. Nolan D, Watts GF, Herrmann SE, French MA, John M, Mallal S, et al. Endothelial function in HIV-infected patients treated with protease inhibitors. AIDS 2000;14:F123-8.
19. Blanco JJ, García IS, Cerezo JG, de Rivera JM, Anaya PM, Raya PG, et al. Endothelial function in HIV-infected patients with low or mild cardiovascular risk. J Antimicrob Chemother 2006;58:133-9.
20. Bressollette L, Roudaut N, et al. Increased risk of myocardial infarction with HIV infection: Traditional risk factors overshadow impact of protease inhibitor exposure. AIDS 2005;19:927-33.
21. Depaireon M, Chessex S, Sudre P, Rodondi N, Doser N, Chave JP, et al. Premature atherosclerosis in HIV-infected individuals – Focus on protease inhibitor therapy. AIDS 2001;15:329-34.
22. Nolan D, Watts GF, Herrmann SE, French MA, John M, Mallal S, et al. Endothelial function in HIV-infected patients receiving protease inhibitor therapy: Does immune competence affect cardiovascular risk? QJM 2003;96:825-32.
23. Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, et al. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. Circulation 2004;104:257-62.
24. van Wijk JP, de Koning EJ, Cabezas MC, Joven J, opt’Roodt J, Rabelink TJ, et al. Proteinuria and its relation to cardiovascular disease. Int J Nephrol Renovasc Dis 2003;43:1482-9.
25. Chaparro AI, Mitchell CD, Abitbol CL, Wilkinson JD, Bressollette L, et al. Subclinical carotid atherosclerosis in HIV-infected individuals – Focus on protease inhibitor therapy. AIDS 2001;15:329-34.
26. Ugboma H, et al. Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses. AIDS 2006;20:2275-83.
27. Jericó C, Knobel H, Calvo N, Sorli ML, Guelar A, Gimeno-Bayón JL, et al. Subclinical carotid atherosclerosis in HIV-infected patients: Role of combination antiretroviral therapy. Stroke 2006;37:812-7.
28. Maggi P, Perilli F, Lillo A, Gargiulo M, Ferraro S, Grisorio B, et al. Rapid progression of carotid lesions in HAART-treated HIV-1 patients. Atherosclerosis 2007;192:407-12.
29. Mangili A, Gerrior J, Tang AM, O’Leary DH, Polak JK, Schaefer EJ, et al. Risk of cardiovascular disease in a cohort of HIV-infected adults: A study using carotid intima-media thickness and coronary artery calcium score. Clin Infect Dis 2006;43:1482-9.
30. Currier JS, Kendall MA, Zackin R, Henry WK, Alston-Smith B, Torriani FJ, et al. Premature atherosclerosis in HIV-infected individuals – Focus on protease inhibitor therapy. AIDS 2001;15:329-34.
31. Nolan D, Watts GF, Herrmann SE, French MA, John M, Mallal S, et al. Endothelial function in HIV-infected patients receiving protease inhibitor therapy: Does immune competence affect cardiovascular risk? QJM 2003;96:825-32.
32. Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, et al. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. Circulation 2004;104:257-62.
33. van Wijk JP, de Koning EJ, Cabezas MC, Joven J, opt’Roodt J, Rabelink TJ, et al. Proteinuria and its relation to cardiovascular disease. Int J Nephrol Renovasc Dis 2003;43:1482-9.
27. Emem CP, Arogundade F, Sanusi A, Adelusola K, Wokoma F, Akinsola A, et al. Renal disease in HIV-seropositive patients in Nigeria: An assessment of prevalence, clinical features and risk factors. Nephrol Dial Transplant 2008;23:741-6.

28. Agaba EI, Agaba PA, Sirisena ND, Anteyi EA, Idoko JA. Renal disease in the acquired immunodeficiency syndrome in North central Nigeria. Niger J Med 2003;12:120-5.

29. Odueyungbo A, Smieja M, Thabane L, Smaill F, Gough K, Gill J, et al. Comparison of brachial and carotid artery ultrasound for assessing extent of subclinical atherosclerosis in HIV: A prospective cohort study. AIDS Res Ther 2009;6:11.

30. Gupta SK, Mather KJ, Agarwal R, Saha CK, Considine RV, Dubé MP, et al. Proteinuria and endothelial dysfunction in stable HIV-infected patients. A pilot study. J Acquir Immune Defic Syndr 2007;45:596-8.