

Case report

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Hypertriglyceridemia in Antiretroviral Therapy

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Introduction

Elevated serum triglycerides, total cholesterol, very low-density lipoprotein (VLDL) cholesterol, and low-density lipoprotein (LDL) cholesterol have been reported in the literature from areas where experience with antiretroviral drugs has amassed. Up until recently the use of antiretroviral drugs in Nigeria on a wide scale was a rarity owing largely to prohibitive cost, and so experience with its use was limited. Here we report 3 cases out of 11 followed up on antiretroviral drugs for a period of 6 months (June to November 2002) who had a steady rise in serum triglyceride level, as part of the initial 25 trial patients on free antiretroviral drugs supplied by the Nigerian federal government as a pilot study an accelerated clinical trial of a combination of stavudine/lamivudine/nevirapine in the treatment of people living with HIV/AIDS in Nigeria at the University of Benin teaching hospital, one of the designated centers for the treatment of HIV/AIDS.

Methods

All patients met the study's eligibility criteria and signed an informed consent form; the study was approved by the University teaching Hospital's committee on ethics. All laboratory tests, which included serum amylase, liver enzymes and bilirubin, triglyceride levels, hemoglobin levels, complete blood count, and CD4+ cell count, were done at the teaching hospital's main laboratory, and blood samples for triglycerides were all obtained in the fasting state, CD4+ cell count was determined by flow cytometry. All laboratory tests were repeated at intervals of 4 weeks throughout the duration of the study.

Eligibility Criteria

Inclusion Criteria

1. Older than 15 years of age
2. HIV seropositivity by double enzyme-linked immunosorbent assay (ELISA) or ELISA and Western blot
3. Willingness to give informed consent
4. Willingness to show up for follow-up visits
5. HIV RNA level > 5000 copies/mL
6. CD4+ cell count of 100-400 cells/microliter (mCL)
7. Patient must be antiretroviral-drug-naive
8. Patient must be willing to continue therapy after the trial
9. Female patient must be willing to use an adequate and reliable method of contraception

Exclusion Criteria

1. Younger than 15 years of age
2. Pregnant patients or nursing mother
3. Neutrophil count < 1000/mCL
4. Severe liver or renal disease

5. Patient on rifampicin or rifabutin therapy

Results**Case 1**

O.P., a 35-year-old male commercial driver, was enrolled in the treatment study group with a body weight of 69.5 kg and a body mass index (BMI) of 24 kg/m² (his height was 1.70 m). His CD4+ cell count at commencement was 100 cells/mcL and fasting serum triglyceride was 108 mg/dL. After 8 weeks of therapy, weight was 70.5 kg and serum triglyceride was 122 mg/dL. At 16 weeks he weighed 73 kg and triglyceride had risen to 265 mg/dL. At 24 weeks (end of study), he weighed 74.5 kg and serum triglyceride was 300 mg/dL; CD4+ cell count had risen to 300 cells/mcL. CD4+ cell counts at 4, 8, 12, 16, and 20 weeks, respectively, were 109, 215, 260, 272, and 292 cells/mcL.

Case 2

O.W., a 22-year-old female University student, was commenced on treatment with a body weight of 57 kg and a BMI of 20.4 kg/m² (her height was 1.67 m). Her CD4+ cell count was 310 cells/mcL and she had a fasting serum triglyceride of 169 mg/dL. At 8 weeks of therapy she weighed 67.6 kg and the serum triglyceride had risen to 200 mg/dL. After 12 weeks of therapy, her weight was 71 kg, with a CD4+ cell count of 482 cells/mcL and serum triglyceride of 210 mg/dL. At 16 weeks she weighed 71.5 kg and the triglyceride level was 220 mg/dL. At 24 weeks (end of study), body weight was 73 kg, CD4+ cell count was 490 cells/mcL, and triglyceride level was 214 mg/dL. CD4+ cell counts at 4, 8, 12, 16, and 20 weeks, respectively, were, 315, 350, 415, 445, and 460 cells/mcL.

Case 3

O.A., a 44-year-old male commercial driver, was enrolled in the treatment group with a body weight of 106.5 kg and a BMI of 34.8 kg/m² (height of 1.75 m), with CD4+ cell count of 390 cells/mcL and triglyceride of 147 mg/dL. After 8 weeks of therapy, body weight was 108 kg and triglyceride level was 240 mg/dL. At 12 weeks, body weight was 110 kg, CD4+ cell count had risen to 402 cells/mcL and triglyceride level was 316 mg/dL. At 16 weeks, weight was 111.5 kg and serum triglyceride was 317 mg/dL. At 24 weeks (end of study), body weight was 111.5 kg, CD4+ cell count was 423 cells/mcL, and serum triglyceride was 448 mg/dL. CD4+ cell counts at 4, 8, 12, 16, and 20 weeks were, 394, 398, 410, 418, 420 cells/mcL, respectively.

All 3 patients were referred to the endocrinology unit for evaluation and treatment on account of elevated (> 200 mg/dL) fasting triglyceride level. Essentially all study subjects had serum amylase levels within normal limits throughout the duration of study.

Discussion

Highly active antiretroviral therapy (HAART) has been associated with hypertriglyceridemia, lipodystrophy, hypercholesterolemia, and insulin resistance, a syndrome referred to variously as HAART-associated morphologic and metabolic abnormality syndrome (HAMMAS) or HIV-associated lipodystrophy syndrome. Initially the protease inhibitors were implicated but it has been reported with the use of other classes of antiretroviral drugs.[1,2]

All patients in this study were on lamivudine/stavudine/nevirapine (nucleoside and nonnucleoside reverse transcriptase inhibitors only). The progressive increases in body mass index and CD4+ cell count were measures of good response to therapy. The inclusion of nevirapine in the regimen is noteworthy owing to its widely reported beneficial effect on blood lipid profile[3-5] by increasing the HDL cholesterol levels as compared with protease inhibitors, though this relative advantage was not proven in a related study involving older subjects,[6] and in another study, the lipid profile of patients on nevirapine was worse compared with HAART-naive subjects.[4] This is not to say that nevirapine is the definite cause of the deranged triglyceride levels, but to mention curiously that in drug combinations devoid of a protease inhibitor, lipid abnormality (raised triglyceride in this case) is being seen.

The possibility exists here that stavudine, a drug associated with hepatic steatosis,[1] may be the culprit, but to mention it as a definite cause also would be preliminary. Patients on stavudine did not fare worse in blood lipid parameters compared with zidovudine, another nucleoside analogue reverse transcriptase inhibitor, in a related study comparing both in antiretroviral therapy and blood lipid profile.[7] The exact contribution of stavudine in deranged lipid profile remains to be proven, but now that it is regularly a part of HAART prescriptions in Nigeria, this may be known with time.

It is also pertinent to discuss the possible role of pancreatitis, a condition that has a cause-and-effect relationship with hypertriglyceridemia, particularly in its chronic forms in which serum amylase levels may be within normal limits,[8] as was found in our study patients. In patients who had normal triglyceride levels at the commencement of study and who were never on didanosine, a drug known to be associated with pancreatitis, and who were noticed to have elevated triglyceride levels as early as 4 weeks on HAART, it would not be immodest to associate the rise with the drugs.

The implication of HAART-induced dyslipidemia in cardiovascular terms is a growing cause for concern against the backdrop of a continuous therapy, even though the risk remains to be established.[9-11] Certainly more informa-

tion will be revealed as other lipid parameters are studied subsequently.

As yet there appears to be no consensus on the use of hypolipidemic agents in HAART-induced hyperlipidemia, and further studies are needed to establish this.[9-12] Regular follow-up, however, is strongly advised, particularly in subjects with other risk factors for coronary artery disease.

Conclusion

That dyslipidemia is a known consequence of HAART should sensitize regular monitoring of triglyceride and other indices of lipid profile in individuals on HAART, with a view to instituting therapy as early as possible when values are found deranged, particularly in those with other risk factors for coronary artery disease.

Authors and Disclosures

Frank Aiwansoba Imarhiagbe, MBChB, FMCP, has disclosed no relevant financial relationships.

Emmanuel Pandy Kubeyinje, MBBS, FRCP, has disclosed no relevant financial relationships.

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