Non-alcoholic fatty liver disease in HIV-infected patients without viral hepatitis
What can we do about their cardiovascular risk?

Μη αλκοολική λιπώδης νόσος του ήπατος σε ασθενείς με λοίμωξη HIV χωρίς ιογενή ηπατίτιδα C
Τι μπορούμε να κάνουμε για τον καρδιαγγειακό τους κίνδυνο;

**G. Sfikas, Chr. Boutari,
K. Tassios, K. Kaitanidis,
E. Mitsiou, V.G. Athyros**

*2nd Propedeutic Department of Internal Medicine,
Medical School, Aristotle University of Thessaloniki,
"Hippocration" Hospital, Thessaloniki, Greece*

**Γ. Σφήκας, Χρ. Μπουτάρη,
Κ. Τάσιος, Κ. Καϊτανίδης,
Ε. Μήτσιου, Β.Γ. Άθυρος**

*Β΄ Προπαιδευτική Παθολογική Κλινική,
Ιατρική Σχολή, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης,
«Ιπποκράτειο» Νοσοκομείο, Θεσσαλονίκη*

ABSTRACT: Life expectancy of HIV-infected persons has been extended by current treatment of the disease. Thus, other causes of morbidity and mortality in these patients have emerged. Liver disease was identified as a leading cause of death among HIV-infected persons and this became evident during the recent years. Non-alcoholic fatty liver disease (NAFLD) is the leading cause of liver disease in the general population and even more in HIV-infected patients. There is no generally accepted treatment for NAFLD; however, it has been shown that statin treatment is beneficial treatment of NAFLD within a multifactorial approach of the disease or even in monotherapy. The issue is that this treatment has not yet been tested in HIV-infected persons. Thus, the logical suggestion is to try this treatment in HIV patients with NAFLD,

ΠΕΡΙΛΗΨΗ: Το προσδόκιμο ζωής των προσβεβλημένων ατόμων από HIV έχει παραταθεί σημαντικά με τις θεραπείες της νόσου που εφαρμόζονται τα τελευταία χρόνια. Έτσι έχουν προκύψει άλλες αιτίες νοσηρότητας και θνητότητας σε αυτούς τους ασθενείς. Τα ηπατικά νοσήματα αποτελούν μια από τις κύριες αιτίες θανάτου μεταξύ των προσβεβλημένων ατόμων από HIV και αυτό έγινε εμφανές κατά τη διάρκεια των τελευταίων ετών. Η μη αλκοολική λιπώδης νόσος του ήπατος (ΜΑΛΝΗ) είναι η κύρια αιτία της ηπατικής νόσου στον γενικό πληθυσμό και ακόμη περισσότερο σε άτομα προσβεβλημένα από HIV. Δεν υπάρχει καμία γενικά αποδεκτή θεραπεία για τη ΜΑΛΝΗ. Ωστόσο, έχει δειχθεί ότι η θεραπεία με στατίνες είναι ευεργετική στη ΜΑΛΝΗ στα πλαίσια μιας πολυπαραγοντικής προσέγγισης της νόσου ή ακόμη και σε μονοθεραπεία. Το θέμα

Vasilios G. Athyros, MD, FESC, FRSPH, FASA, FACS
15 Marmara street, GR-551 32 Thessaloniki, Greece
Tel: (+30) 2310-892 606, Fax: (+30) 2310-835 955
e-mail: vathyros@gmail.com – athyros@med.auth.gr

Βασίλειος Γ. Άθυρος, MD, FESC, FRSPH, FASA, FACS
Μαρμαρά 15, 551 32 Θεσσαλονίκη
Τηλ: 2310-892 606, Fax: 2310-835 955
e-mail: vathyros@gmail.com – athyros@med.auth.gr

given that these patients are exposed to high cardio-vascular disease risk, and thus statin treatment might be beneficial in multiple ways. Given that not all but specific statin compounds at specific doses are effective in NAFLD treatment, prospective, randomized, controlled studies should be undertaken to prove effectives of statin treatment on HIV-infected persons with NAFLD.

είναι ότι αυτή η θεραπεία δεν έχει ακόμη δοκιμαστεί σε άτομα προσβεβλημένα από HIV. Έτσι, η λογική πρόταση είναι να δοκιμαστεί αυτή τη θεραπεία σε ασθενείς με HIV που έχουν ΜΑΛΝΗ. Δεδομένου ότι αυτοί οι ασθενείς είναι εκτεθειμένοι σε υψηλό κίνδυνο καρδιαγγειακής νόσου, οι στατίνες μπορεί να είναι επωφελείς με πολλούς τρόπους. Δεδομένου ότι δεν είναι όλες οι στατίνες που απεδείχθησαν ότι συμβάλλουν στην αντιμετώπιση της ΜΑΛΝΗ, αλλά συγκεκριμένες στατίνες και σε συγκεκριμένες δόσεις είναι αποτελεσματικές στη θεραπεία της ΜΑΛΝΗ, προοπτικές, τυχαιοποιημένες, ελεγχόμενες μελέτες θα πρέπει να αναλάβουν την υποχρέωση να αποδείξουν την αποτελεσματικότητα της θεραπείας με στατίνες σε άτομα προσβεβλημένα από HIV.

Key words: HIV, NAFLD, NASH, morbidity, mortality, treatment.

Λέξεις ευρετηρίου: HIV, NAFLD, NASH, νοσηρότητα, θνητότητα, θεραπεία.

Non-alcoholic fatty liver disease (NAFLD), a term describing the most common liver disease, which is characterized by accumulation of fat (>5%) in liver cells in the absence of excessive alcohol intake, chronic viral hepatitis or other liver disease.[1,2] NAFLD prevalence in the general population in Western Countries varies from 14% to 31%.[3] Histological manifestation of NAFLD ranges from simple steatosis to steatohepatitis (NASH characterized by hepatocellular necroinflammation and ballooning with or without liver fibrosis), and cirrhosis, which in some cases may progress to hepatocellular carcinoma.[4] Data suggests that NASH prevalence ranges from 3–5% (>20% of NAFLD cases) in the general population, however this rises to 37% in the morbidly obese.[4] NAFLD/NASH is considered as the hepatic manifestation of metabolic syndrome (MetS), and is closely related to cardiovascular disease (CVD) risk,[5] to the extent that NAFLD/NASH and CVD are viewed as two aspects of a shared disease.[5,6] The United States (US) National Health and Nutrition Examination Survey (NHANES) was conducted in 1988–1994 and followed-up 11,154 participants until the end of 2006 (mean follow up of 15 years). The findings suggest that the degree of liver fibrosis is related to clinical outcome in NAFLD/NASH patients.[6] The 15 year follow-up showed that NAFLD in the form of steatosis was not related with higher total mortality compared with those without NAFLD, however, there was a progressive substantial increase in total mortal-

ity with increasing levels of non-invasive liver fibrosis scores as compared with subjects without fibrosis.[6] The increase in mortality was mainly due to increased CVD mortality.[6] As a consequence, NAFLD/NASH with fibrosis have been identified as independent CVD risk factors.[5,6]

Seeing that HIV-infected persons are experiencing a longer life expectancy,[7] other causes of morbidity and mortality among this group are increasingly being acknowledged. Recently, liver disease was identified as a leading cause of death among HIV-infected persons.[8,9] Some studies suggest that NAFLD is common among HIV-infected, HCV-seronegative patients, however, its prevalence is related with NAFLD risk factors and not with HIV infection per se or with antiretroviral therapy.[10] Nevertheless, this became a matter of debate because other studies did not confirm this finding.[11] Exposure to highly active antiretroviral therapy (HAART), especially nucleoside reverse-transcriptase inhibitors (NRTI) was an independent risk factor for NAFLD, with an 11% increase in the odds ratio for each year of treatment.[11] Moreover, data from 17,852 subjects enrolled in the Data collection on Adverse events of Anti-HIV Drugs (DAD) study, a prospective multinational cohort study initiated in 1999, suggest that those on a combination of a protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) experienced lipid profile abnormalities and

increased CVD risk.[12] Very recent data suggest that HIV patients are exposed to a higher risk of adverse CVD events. This is probably due to complex interactions between traditional risk factors and HIV infection itself through endothelial dysfunctional leading to immune activation of inflammation and increased risk of thrombosis. On the other hand long-term antiretroviral therapy seems to play an adverse role also.[13] These substantially increase the CVD death/AIDS death ratio.[13] Within this frame, the selection of the appropriate antiretroviral regimens can play a major role in managing CVD risk when initiating or switching treatments.[14] Also, antiretroviral drugs with favorable lipid profiles (i.e. nevirapine) may help.[14,15] Thus, switching from a PI therapy to a virologically successful regimen of a potent once-daily drug with neutral or favourable effect on lipid profile (i.e. efavirenz), resulted in an improvement of fasting total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), and, more important, the cholesterol/high-density lipoprotein cholesterol (HDL-C) ratio.[16] In this context prevention or treatment of NASH with fibrosis might be another important aspect in the effort to reduce CVD risk in HIV-infected patients.

Recently, a study from the University of San Diego, California, presented data from a 13-year follow-up of HIV patients with a biopsy proven NAFLD.[16] Identification of HIV related NAFLD in long-term HIV-infected patients was made after exclusion of other causes of liver disease and hepatic steatosis.[17] Age and sex-matched controls with biopsy-proven primary NAFLD not infected by HIV were selected from the same pathology database.[17] As compared to age and sex-matched NAFLD controls, patients with HIV-associated NAFLD had significantly higher rates of NASH (63% *vs* 37%, p=0.04), and more features of liver injury, including lobular inflammation (<0.001) and acidophil bodies (<0.001).[17] Serum triglycerides were higher (p=0.024) in HIV-associated NAFLD patients than in controls, and all liver enzyme activities were also higher; aspartate aminotransferase (ALT) (p<0.001), alanine aminotransferase (AST) (p<0.001), alkaline phosphatase (AP) (p=0.003).[17] These data suggest that HIV-associated NAFLD is related with increased severity of liver disease and a higher incidence of NASH compared to age and sex-matched NAFLD controls.[17] Authors also report that patients with NASH and severe fibrosis had a longer exposure both to the disease.[17,18] and to antiretroviral therapy (107 *vs* 34 months, p=0.007).[19]

Given that NAFLD/NASH, especially with fibrosis, are considered as high CVD risk factors, to the degree that there are suggestions that NAFLD/NASH should be considered as a coronary heart disease equivalent,[20] there is an urgent need for an effective treatment.[20] Lifestyle changes are the first line intervention for both NAFLD/NASH and MetS,[21] however there is limited compliance on a long term basis.[21] In regard to NAFLD treatment in general, insulin sensitizers (thiazolidinediones), antioxidants (vitamin E), lipid-lowering drugs, pentoxifylline, angiotensin receptor blockers, and n-3 fatty acids show some promise.[22] However, there is a lack of consensus regarding the appropriate pharmacotherapy for NAFLD/NASH. Animal studies suggest that herbal medicines and natural products may be promising therapeutic agents for NAFLD/NASH, but their efficacy and safety has not yet been investigated in human studies.[22]

It seems that there are data about the beneficial effect of statins on NASH. These come either from small studies or from post hoc analyses of larger randomized prospective studies; thus these data have not been generally accepted yet. Five years ago, the post hoc analysis of the Coronary Heart Disease Evaluation (GREACE) survival study (n=1,600; 437 patients had moderately abnormal liver tests at baseline, probably due to NAFLD as indicated by liver ultrasonography and after exclusion of other liver diseases)[23] showed that 227 participants who were treated with statins (mainly atorvastatin, mean dose 23 mg/day) had a substantial improvement in liver tests, ALT, AST, and gamma-glutamyl transpeptidase (GTT) (p<0.0001), whereas 210 not treated with a statin had a further increase of liver enzyme concentrations.[23] Statin treatment was safe in patients with CVD and NAFLD; only 1% discontinued treatment.[23] Thus, atorvastatin did not have any adverse effect on liver enzymes; on the contrary it reduced them substantially and improved liver ultrasonography within the 3-year duration of the study.[23] Moreover, atorvastatin reduced CVD events substantially more in NAFLD/NASH patients *vs* usual care (69%) than in those without NAFLD/NASH vs usual care patients (38%, p=0.007 *vs* NAFLD patients).[23]

Four years ago a study with pitavastatin (2 mg/day administered for 12 months) in 20 patients with biopsy-proven NASH with dyslipidaemia was published.[24] Liver enzymes and lipid profile were significantly improved, however NAFLD/NASH activity score and fibrosis stage did not change significantly in all patients (they improved in 54% and 42%, respectively) and 3 of

the 13 patients with a repeat biopsy had progression of fibrosis during the treatment.[24]

Three years ago a study included 42 biopsy-proven NASH patients treated with atorvastatin 10 mg/day for 12 months. Atorvastatin significantly decreased liver transaminase, GGT, LDL-C, TGs, type IV collagen, and tumor necrosis factor (TNF) - alpha levels, while it improved NAFLD activity score and increased the liver to spleen density ratio.[25]

During the same year a prospective study that investigated the effect 2.5 mg/day rosuvastatin for 24 months in 19 patients with biopsy-proven NASH with dyslipidaemia was published.[26] Transaminase levels, relatively low at the beginning, were not significantly changed during the treatment, while lipid profile was significantly improved.[26] In these patients NAFLD activity score and fibrotic stage did not change significantly in all patients, they were improved in 33% and 33% of patients, and remained stable in 33% and 56% of patients, respectively, while 1 of 9 patients had progression of fibrosis during rosuvastatin treatment.[26] This partially beneficial result was attributed to the very low dose of rosuvastatin administered (2.5 mg/day).[26] During the same year a post hoc analysis of the survival study Assessing the Treatment Effect in Metabolic Syndrome Without Perceptible Diabetes (ATTEMPT) (n=1,123)[27] with an atorvastatin based multifactorial treatment approach in Greek patients and MetS and NAFLD showed that attaining multiple treatment targets is safe and beneficial in primary prevention patients with MetS and NAFLD/NASH.[27] Lipid levels and liver enzymes were normalized and ultrasonographic evidence of NAFLD resolved during the 42 month duration of the study in both intensive (mean dose 34 mg/day) and standard (mean dose 24 mg/day) atorvastatin treatment groups.[27]

In 2013 the post hoc analysis of the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial (n=8,863) was published.[23] From patients 1,081 (12.2%) had NAFLD/NASH; 558 were assigned to simvastatin 20–40 mg/day and 523 to atorvastatin 80 mg/day.[28] Five year results showed that high dose atorvastatin treatment (80 mg) in patients, who had an ALT≥ULN resulted in normalisation of ALT values.[28] The high atorvastatin dose (80 mg/day) induced a greater reduction in liver enzyme activities as compared with the moderate simvastatin dose of 20–40 mg/day.[28] In these patients with evidence of NAFLD/NASH, major CVD event rates were 11.5% for simvastatin and 6.5%

for atorvastatin, indicating a significant CVD risk reduction with intensive statin therapy (hazard ratio, 0.556; 95% confidence interval, 0.367–0.842; p=0.0056).[28] Thus, aggressive statin treatment with a high potency statin halved the CVD event rate in patients with NAFLD/NASH during a five year follow-up.[28]

In 2014 a pilot study (n=6) with 10 mg/day of rosuvastatin monotherapy in biopsy proven NASH patients with MetS, showed within one year of treatment a normalisation of lipid profile, all liver enzymes, and complete resolution of NASH in the repeat biopsy (fibrosis, necroinflammation, ballooning, and steatosis were totally absent and histology revealed a normal liver tissue) in 5 out of 6 patients.[29] The study for which the pilot was designed was completed in 2015, and reported data on all 20 biopsy proven (repeat biopsy after 12 months of treatment) NASH patients with MetS treated with rosuvastatin monotherapy of 10 mg/day.[30] The results remained as impressive as in the pilot study, complete resolution of NASH, while no patient had MetS by the end of the study.[30] The results also showed that all 20 patients did not have MetS any longer, due to the reduction in TGs, the increase in HDL-C, and a paradoxical (substantial by 20 mg/dL) reduction in fasting plasma glucose.[30] Exercise and diet and consequently waist circumference and body mass index did not change, thus, the improvement could not be attributed to reduction of (abdominal) obesity.[30] The most probable cause for this paradoxical finding is that resolution of NASH by rosuvastatin, an insulin resistance state, improved glucose metabolism.

All the above suggest that statins are safe in NAFLD/NASH patients, and specific statins at appropriate doses can resolve NAFLD/NASH, substantially reducing CVD risk at the same time.[31] Dyslipidemia in HIV patients is different from the general population, due to the fact that HIV treatment may not only cause dyslipidemia, but may also interact with lipid lowering medication.[32] Current guidelines recommend the use of pravastatin and atorvastatin as first-line therapy, while European guidelines include rosuvastatin also.[32] The addition of ezetimibe, fenofibrate or fish oil in unresponsive to statins patients or in those with atherogenic mixed hyperlipidaemia is also recommended.[32] There is a need to investigate if the use of statins in HIV-dyslipidemia is associated with an increase in the new onset diabetes, given that HIV patients are known to be insulin-resistant; HIV is also associated with NAFLD, a condition known to be associated with insulin resistance.[32] The effect of statins on the im-

mune system of HIV patients has also been tested. Atorvastatin was associated with a significant reduction in CD8 T-cell activation (HLA-DR, CD38/HLA-DR) and exhaustion (TIM-3, TIM-3/PD-1), whereas pravastatin had no effect.[33] In contrast, pravastatin increased antigen specific interferon γ production,[33] suggesting that there are differential effect of statins on immune activation and function.[33] Immune activation and chronic inflammation are recognized as major component of HIV disease even in patients with undetectable viral load. CD38 activation was significantly lower after 48 weeks of treatment with atorvastatin, with no difference in high-sensitivity C-reactive protein and CD4,[34] suggesting that atorvastatin reduces the level of immune activation even in patients with undetectable viral load.[34] These off target effects of atorvastatin to reduced T-cell immune activation and exhaustion among HIV patients treated with combined AntiRetroviral Treatment (cART) made atorvastatin a candidate for adjunct therapy in a strategy to improve HIV treatment outcomes.[35] In clinical care, atorvastatin and rosuvastatin are preferable to pravastatin for treatment of HIV-infected patients with dyslipidaemia, due to greater declines in total cholesterol, LDL-C, and non-HDL-C, with similar lower toxicity rates, mainly due to interactions with anti HIV drugs.[36]

It has been reported that in HIV-infected patients the prevalence rates of for hypertension, dyslipidemia, and diabetes are 26%, 48%, and 13%, respectively.[37] NAFLD/NASH has a higher prevalence in HIV patients than in general population.[17] However, these CVD risk factors are modifiable and effective treatment of related comorbidities may improve morbidity and mortality in HIV-infected patients.[37] HIV patients need statin treatment because they are exposed at a high CVD risk.[12–14] It would be wiser to select high intensity statins (atorvastatin or rosuvastatin) at high doses in order to treat dyslipidemia, possibly resolve NAFLD/NASH and MetS, and take advantage of their off target effects on the immune system and leukocyte activation.[33,34]

In a very recent retrospective analysis of 438 cART treated HIV patients from the Nutrition For Healthy Living (NFHL) cohort were used to determine the association between statin treatment (67 were on statins) and incidence of myocardial infarction (MI), stroke, and all-cause mortality as a composite endpoint.[38] Results showed that statins did not have an effect on MI, stroke, and mortality.[38] On the contrary CD4 count appeared to be an important predictor of all these outcomes, even after exclusion of death from the composite endpoint.[38] However, this was a retrospective study, only a few patients were on statins, statin compounds and doses as well as the attainment of LDL-C goal are not reported.[38]

There have been no studies with statins in HIV infected patients with NAFLD/NASH, in terms of investigating the actual effect of statins on CVD risk reduction in this specific population, nevertheless, this seems to be a very good idea and should be attempted. However, these studies should have a prospective, long-term, randomized, controlled design with the use of high potency statins at appropriate doses to reach lipid goals and enough participants to ensure statistical power able to show clinical benefit and resolution of NAFLD/NASH or/and MetS if present.

Declaration of interest

There is no conflict of interest for all authors.

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