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CORRELATIONS BETWEEN VIRO-IMMUNOLOGIC STATUS OF THE NEWLY DIAGNOSED PATIENT WITH HIV INFECTION AND LIVER DAMAGE

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ABSTRACT

Liver damage can be a direct consequence of human immunodeficiency virus infection or indirect mechanisms triggered by human immunodeficiency virus. Hepatic fibrosis may be present in patients newly diagnosed with HIV infection or in those with viro-immunologic failure after initiation of antiretroviral therapy. In the present study we evaluated biologically and viro-immunologically the 351 patients newly diagnosed with HIV infection in the Regional Center Constanta between 01.01.2015 and 31.06.2024, subsequently re-evaluated one year after diagnosis and institution of specific medication. Liver fibrosis stage was assessed using APRI, FIB4 and FORNS scores. The cohort comprised 351 patients, 313 with HIV monoinfection. The mean age at diagnosis was 36.09 years, predominantly male (237 patients). The median CD4+ cell count was 269.5 cells/mm3, and the median HIV-RNA was 164 x103 copies/mL. Most cases were CDC staged A2 (91 cases) and C3 (77 cases). Patients with HIV monoinfection showed a significant association between CD4+ cell level and ALT ($p=0.026$) and AST ($p<0.001$), respectively. We observed statistically significant correlation between AST and viral load values ($p=0.003$ in monoinfection and 0.042 in coinfection). APRI, FIB4 and FORNS scores averaged higher in the coinfected group compared to the HIV monoinfected group. Statistically significant associations were found between APRI, FIB4, FORNS scores and CD4+ cell counts and HIV viral load values, respectively.

Keywords: HIV, CD4+, ARN-HIV, APRI, FIB4, FORNS.

Introduction

Human immunodeficiency virus infection is a global public health problem. Following the introduction of active antiretroviral therapy in the mid-1990s, HIV infection, although incurable, has become a chronic infection. Depending on the degree of immunosuppression it causes, it leads to multi-system damage. Chronic liver damage is currently one of the main causes of mortality and morbidity, as well as of discontinuation of therapy in these patients.

Chronic inflammation of the liver, secondary to HIV infection per se or in association with exposure to other risk factors, will lead to liver fibrosis, which is the main risk factor for liver disease progression. Therefore, the early recognition and diagnosis of liver involvement in this patient population is a desideratum to ensure improved quality of life, morbidity and mortality in.

Several clinical and epidemiologic studies have reported that HIV per se induces hepatic fibrogenesis (1). Thus, detectable viremia is essential to determine liver damage (2). In addition, mathematical modeling of liver enzyme increases in HIV monoinfection has demonstrated that a significant increase in ALT correlates with increased viral load (3).

Data from CFAR (Center for AIDS Research) revealed that untreated HIV monoinfection is an independent risk factor for liver fibrosis (4).

A large clinical trial conducted in North America showed that in patients with HIV monoinfection, elevated plasma HIV-RNA levels were associated with significant fibrosis (F4) (5).

The association between detectable HIV-RNA and APRI score values above 1.5 directly correlates with the risk of developing liver disease and significant liver fibrosis (6).

In another study, cross-sectional, CD4+ level less than 200 cells/ mm3 was found to be predictive of abnormal liver stiffness (7).

Material and methods

We conducted a prospective, longitudinal study in which we included all patients, aged at least 18 years, newly diagnosed with HIV infection, at the Regional Center Constanța, between January 01, 2015 and June 30, 2024. The study group comprised a total of 351 patients, of which 313 with HIV monoinfection, 37 with HIV/ hepatitis co-infection (HIV/HBV - 21 patients, HIV/HCV - 15 patients, HIV/HBV/HCV - one patient), one patient with undetermined serologic status for HBV, HCV (died in the immediate period of diagnosis).

For each patient we collected the following data at the time of diagnosis and then at the 1-year follow-up: year of diagnosis, personal data (sex, age, urban/rural), HIV infection status, biochemical data (ALT, AST, GGT, platelets, total cholesterol) to calculate liver fibrosis scores (APRI, FIB4, FORNS), virological data (HBsAg, HCV-Ab, HIV-RNA), CD4+ cell count, therapeutic regimen instituted. We observed correlations between patients' age, clinical-immunologic stage of HIV infection, the presence of co-infection with hepatitis B and C viruses and CD4+ cells and HIV-RNA values. The degree of liver damage at baseline and then after one year of treatment was assessed using ALT, AST and liver fibrosis scores APRI, FIB4, FORNS. Liver fibrosis stage was assessed using APRI, FIB4 and FORNS score values. We observed correlations between CD4+ cells, HIV-RNA and ALT, AST and liver fibrosis scores at the time of HIV diagnosis. The objective of evaluating patients one year after ART was to observe the evolution of transaminases, CD4+ cells, HIV-RNA and liver fibrosis scores. Suppression of HIV replication was defined for HIV-RNA < 40 copies/mL.

We comparatively analyzed patients with HIV monoinfection versus those with HIV/ hepatitis co-infection.

The descriptive analysis was performed as follows: quantitative variables were presented by value (N), mean, median, minimum and maximum values, and qualitative variables were represented by frequency distribution and percentage. The analysis of association between categorical variables was done using the cross table and $\chi 2$ test (chi-square) or Fisher's exact test. The independent samples t-test was used to compare the means by dichotomous variables. To compare means of parameters between groups we used the ANOVA test. To choose predictors of a particular dependent variable based on statistical criteria we used stepwise multiple regression.

Results

The characteristics of the study patients, at the time of diagnosis, are described in Table I.

Among both women and men, HIV monoinfection was more common than HIV/ hepatitis coinfection (Figure 1).

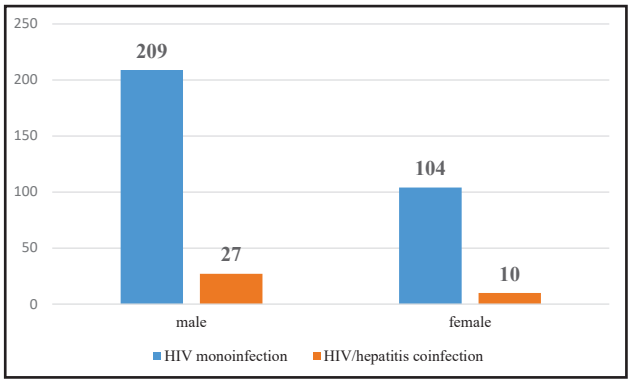

Figure 1 - Sex distribution of cases

Most people (82%) were in the age group 20-49 years.

Table I. Patient characteristics

VARIABLE NAMES	CHARACTERISTICS OF THE GROUP
Total patients	351
HIV monoinfection	342
Age (years) (mean, (min-max))	36.09 (18-73)
Male (N)	237
Urban (N)	242
Year of diagnosis (number of patients)	2015(47), 2016(43), 2017(37), 2018(42), 2019(60), 2020(26), 2021(25), 2022(20), 2023(42), 2024(9)
HIV infection CDC stage (number of patients)	A1(54), A2(91), A3(16), B1(11), B2(44), B3(38),C1(4), C2(13), C3(77)
HIV-RNA<104 (copies/mL) (N)	50
HIV-RNA 104 - 105 (copies/mL) (N)	91
HIV-RNA>105 (copies/mL) (N)	208
Missing HIV-RNA (N)	2
HIV-RNA (copies/mL) (mean, (min-max)) HIV monoinfection	1166315,81 (40 – 29000000)
HIV-RNA (copies/mL) (mean, (min-max)) HIV coinfection HIV/HBV	681375,90 (1998 – 2421951)
HIV-RNA (copies/mL) (mean, (min-max)) HIV coinfection HIV/HCV	424760,73 (2219 – 1370000)
HIV-RNA (copies/mL) (median) (N)	164000
CD4+ (cells/mm3) (median, (min-max)) (N)	269.5 (1 – 1423)
CD4+ <200 (cells/mm3) (N)	67
CD4+ 200-500 (cells/mm3) (N)	149
CD4+ >500 (cells/mm3) (N)	132
CD4+ (cells/mm3) missing	3
HBsAg positive (N)	22
HCVAb positive (N)	16
INSTI treatment (N)	214
NRTI treatment (N)	331
NNRTI treatment (N)	47
IP treatment (N)	73
ALT (IU/L) increased, HIV monoinfection (N)	80
ALT (IU/L) increased, HIV/hepatitis co-infection (N)	16
ALT (IU/L) (mean, (min-max)) HIV monoinfection	40.1 (5-1226)
ALT (IU/L) (mean, (min-max)) HIV/hepatitis co-infection	50.19 (10-230)
AST (IU/L) increased, HIV monoinfection	85
AST (IU/L) increased, HIV/hepatitis coinfection	16
AST (IU/L) (mean, (min-max)) HIV monoinfection	45.67 (11-1241)
AST (IU/L) (mean, (min-max)) HIV/hepatitis coinfection	48.27 (14-185)
APRI missing , HIV monoinfection (N)	12
APRI (median, (min-max))	0.425 (0.1 – 39.4)
APRI (median, (min-max)) HIV monoinfection	0.31 (0.1 – 39.4)
APRI (median, (min-max)) HIV/hepatitis co-infection	0.54 (0.15 – 18.28)
FIB4 missing, HIV monoinfection (N)	12
FIB4 (median, (min-max))	1 (0.22 - 42.35)
FIB4 (median, (min-max)) HIV monoinfection	0.83 (0.22 – 42.35)
FIB4 (median, (min-max)) HIV/hepatitis co-infection	1.17 (0.29 – 29.95)
FORNS missing, HIV monoinfection	14
FORNS (median, (min-max))	4.03 (0.06 – 15.07)
FORNS (median, (min-max)) HIV monoinfection	3.56 (0.06 – 15.07)
FORNS (median, (min-max)) HIV coinfection	4.5 (0.3-11.41)

Most cases were classified as CDC stage A2 and C3 respectively. (Figure 2)

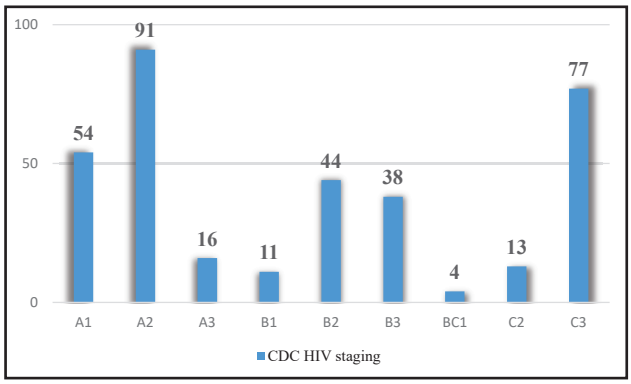

Figure 2. CDC HIV staging

Most patients had CD4+ cell counts between 200-500 cells/mm3 (Figure 3).

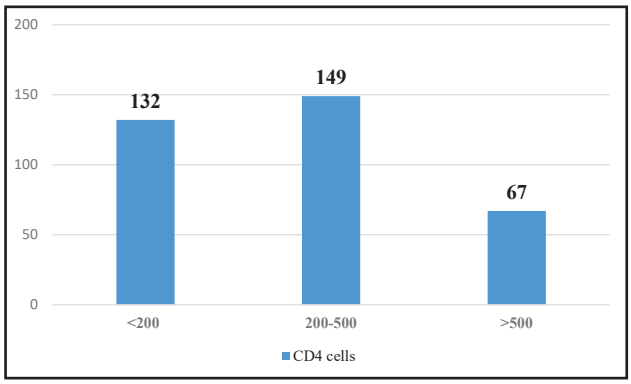

Figure 3. Distribution of CD4 cells counts (cells/mm3)

About 60% of the patients had very high HIV-RNA (>105 copies/mL) and a much smaller percentage (14.3%) had HIV viremia <104 copies/mL.

For the study group, we observed a statistically significant association between age and CDC stage of HIV infection at diagnosis (p=0.009). Cramer's V of 0.192 indicated a moderate association between the two variables.

There was a statistically significant correlation between the patient's age at diagnosis and CD4+ cell count (p=0.003) in the HIV monoinfected group.

We observed that in HIV/hepatitis virus co-infection the immune function is even more impaired, with the majority of patients having CD4+ cells <200/mm3 (56.8%). However, according to the results of ANOVA test, these differences between groups are not statistically significant (p=0.142).

However, there were statistically significant differences between groups in RNA-HIV viral load at diagnosis (F = 3.276 and p = 0.021). Patients co-infected with HIV/hepatitis viruses, especially those with HIV/HBV, are slightly more likely to have a very high viral load at diagnosis.

In the case of HIV monoinfection we identified statistically significant variations in HIV-RNA values between different clinical stages, indicating variability in the severity of HIV infection at diagnosis (F=3.053 and p=0.003).

We observed a higher prevalence of increased ALT and AST for the co-infected group (43.2% versus 26.6% for ALT and 43.2% versus 28.2% for AST).

Patients with HIV monoinfection showed a significant association between CD4+ cell level and ALT (p=0.026) and AST (p<0.001), respectively. For patients with coinfection there was no such association (p=0.287).

There was no statistically significant correlation between HIV-RNA and ALT values in either group (p=0.331 in monoinfection and 0.150 in coinfection). The situation was different for AST, in both groups there was a significant correlation with viral load values (p=0.003 in monoinfection and 0.042 in coinfection).

The APRI, FIB4 and FORNS scores had higher mean scores in the co-infected group compared to the HIV mono-infected group. The p-value of 0.011 for APRI, 0.009 for FIB4 and 0.004 for FORNS indicates that there are statistically significant differences in the mean of these scores in the two categories of patients. Assessing the stages of liver fibrosis, according to the value of these scores, we observed that the majority of patients evaluated were in stage F0F1. However, for coinfected patients, although the majority, F0F1 stage was in a lower percentage compared to monoinfected patients (43.2% versus 67.1% according to APRI score and 59.5% respectively 75.1% according to FIB4 score). The percentage of those with moderate/severe fibrosis was higher in the case of coexisting hepatitis viruses (56.7% respectively 32.9% according to APRI and 40.5% respectively 24.9% according to FIB4). The disadvantage of the FORNS score is that for values between 4.25 and 6.9 it does not

differentiate between liver fibrosis stages.

We identified a statistically significant association between CD4+ cell count and HIV-RNA value and liver fibrosis stage suggested by APRI, FIB4 and FORNS score ($p<0.001$). Cramer's V of 0.258, 0.242 and 0.296 respectively indicated moderate association between variables.

Analyzing the cumulative effect of the predictors (CD4+, HIV-RNA, HIV monoinfection or co-infection with hepatitis viruses) on liver fibrosis scores, we observed that they indicate a significant impact ($p=0.025$) on the APRI score, but the effect is small ($R2 = 0.029$), explaining only 3.4% of the variation in APRI. For the FIB4 score we obtained the same result, p being 0.024, but the effect is small ($R2 = 0.037$), explaining only 4.3% of the FIB4 variation. For the FORNS score, the cumulative effect of the 3 predictors explains 19% of the FORNS variance, p being 0.027.

Regarding the antiretroviral medication instituted, we observed that the most frequently used regimens included NRTIs in combination with INSTIs, with NNRTIs and PIs being less commonly used.

Table II. Patient characteristics after first year

VARIABLE NAMES	CHARACTERISTICS OF THE GROUP
Patients on record	305
HIV mononinfection	275
Male(N)	208
Patients assessed for CD4+ (N)	256
CD4+ (cells/mm3) median, (min-max)	438 (38-1691)
CD4+ <200 (cells/mm3) (N)	114
CD4+ 200-500 (cells/mm3) (N)	105
CD4+ >500 (cells/mm3) (N)	37
Patients screened for HIV-RNA	266
HIV-RNA (copies/mL)(median, (min-max)) HIV monoinfection	<40 (<40, 561.000)
HIV-RNA (copies/mL) (mediana, (min-max)) HIV/hepatitis co-infection	<40 (<40, 1304)
HIV-RNA (copies/mL) <40, HIV monoinfection	187
HIV-RNA (copies/mL)<40, HIV/hepatitis co-infection	15
HIV-RNA (copies/mL)>40, HIV monoinfection	55
HIV-RNA (copies/mL) >40, HIV/ hepatitis co-infection	9
Patients assessed for ALT, AST, APRI, FIB4, FORNS	278
ALT (IU/L) increased, HIV monoinfection (N)(%)	36 (14.5%)
Increased ALT (IU/L), HIV/hepatitis co-infection (N)(%)	8 (27,6%)
ALT (IU/L) (mean, (min-max)) HIV monoinfection	28 (7-266)
ALT (IU/L) (mean, (min-max)) HIV/hepatitis co-infection	37.66 (7-206)
AST (IU/L) increased, HIV monoinfection (N)(%)	23 (9.2%)
AST increased (IU/L), HIV/hepatitis co-infection (N)(%)	7 (24.1)
AST (IU/L) (mean, (min-max)) HIV monoinfection	26.98 (11-380)
AST (UI/L) (mean, (min-max)) HIV/hepatitis co-infection	36.93 (13-173)
APRI (mean, (min-max))	0.26 (0.08 – 4.85)
APRI (median, (min-max)) HIV monoinfection	0.25 (0.08 – 3.95)
APRI (median, (min-max)) HIV/hepatitis co-infection	0.31 (0.12 – 4.85)
FIB4 (median, (min-max))	0.71 (0.16 – 7.20)
FIB4 (median, (min-max)) HIV monoinfection	0.7 (0.16 – 3.79)
FIB4 (median, (min-max)) HIV/hepatitis co-infection	1.02 (0.29 – 7.20)
FORNS (median, (min-max))	2.99 (0.01 – 10.14)
FORNS (median, (min-max)) HIV monoinfection	2.87 (0.01 – 8.37)
FORNS (median, (min-max)) HIV/hepatitis co-infection	3.97 (0.17 – 10.41)

The number of patients remaining at 1 year after diagnosis in the total cohort was 305 (Figure 4).

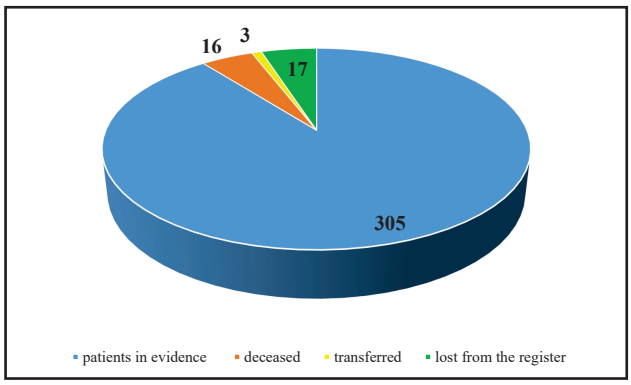

Figure 4. Patients' dynamics 1 year after diagnosis

The characteristics of patients evaluated at 1 year are summarized in Table II.

Analyzing the results obtained at the 1-year assessment, we observed an increase in the number of patients with more than 200 CD4+ cells/mm3 (85.% compared to 62.1% at baseline). 76% of patients had undetectable HIV plasma load. ALT had normal values in 84.2% of patients and AST in 89.2% of patients. We also observed an improvement in the median liver fibrosis scores which equated to an increase in the percentage of patients who were at stage F0F1 (89.6% by APRI score and 88.8% by FIB4 score).

Discussions

From the results, we observed that patients with HIV/hepatitis co-infection, in particular, are slightly more likely to have a very high viral load (>105 copies/mL) at diagnosis.

Although a significant proportion (46.3%) of patients were asymptomatic at the time of HIV diagnosis, categorized as CDC stage A, the majority (80.7%) had low CD4+ cell counts <500/mm3. Moreover, 66.5% of patients diagnosed in clinical stage A had CD4+ cell counts below 500/mm3. Thus, HIV leads to a collapse of the immune system from the asymptomatic phase of infection, and coinfected patients show a more severe impairment of the immune system.

Older patients are more frequently diagnosed at advanced stages of HIV infection, possibly as a consequence of delayed diagnosis or more rapid disease progression.

There are also significant variations in HIV-RNA values between different clinical stages in HIV monoinfection.

As patients get older, they are more likely to have a low CD4+ cell count (<200/mm3).

Elevated ALT values tend to be more common among patients with HIV monoinfection and CD4+ <200 cells/mm3.

HIV viremia is not a significant factor in influencing ALT levels.

Regardless of infection type, a higher HIV-RNA level was associated with a higher risk of increased AST, but the association is stronger in HIV/hepatitis virus coinfection.

APRI, FIB4 and FORNS scores showed significant differences between HIV monoinfected and HIV/hepatitis virus coinfected patient groups, with higher values for coinfected patients.

In HIV monoinfection, as the number of CD4+ cells decreases, APRI, FIB4 and FORNS liver fibrosis scores increase. Also, high HIV viremia values (>105/mm3) as well as more advanced clinical stages of HIV infection are associated with increased values of these scores.

The earliest, even immediate, institution of ART leads to a favorable outcome of patients by restoring the immune system and the undetectability of HIV plasma. Liver function also improves as reflected by mean, median, minimum and maximum ALT, AST and liver fibrosis scores.

Conclusions

In current practice, the degree of liver damage can be assessed using non-invasive imaging techniques, serologic tests and indirect markers that allow immediate, accurate diagnosis. It also offers the possibility of monitoring the evolution of hepatopathy, being simple to repeat.

In terms of HIV infection, the patient's viro-immunologic status, the CDC stage of HIV infection at the time of diagnosis, as well as individual factors (patient's age, presence of comorbidities) determine the different degrees of liver damage.

The institution of antiretroviral therapy tailored to the needs of each patient, immediately

after diagnosis as well as their increased adherence to the prescribed medication improve the patient's immune status in a short time and lead to undetectable plasma HIV and improved or even normalized liver function.

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