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HCV Co-Infection Compromising the Effects of c-ART–An Insight from the HIV-Positive Population in Bulgaria

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Abstract: ***Hepatitis C is common in HIV-positive patients and may considerably impact their prognosis. In Bulgaria, 26% of the HIV+ patients diagnosed between 2010 and 2014 were HCV seropositive, with a very high rate of active co-infections, and multi-risk profile. Immunological and virological parameters (CD4AC, CD4/CD8, HIV viral load) at the time of HIV diagnosis were similar as compared to HIV monoinfection but deteriorated quickly until registration at hospital. Only 52% of HIV+ patients with active HCV infection were started on c-ART. In the absence of HCV-specific therapy, they were characterised by significantly inferior immune restoration (in terms of CD4 AC and CD4/CD8 increase), and lower rate of sustained HIV virologic response (63% vs. 38%; p<0.0001). Altogether, HCV co-infection is a significant risk factor for the progress of HIV epidemics in Bulgaria, and requires specific efforts for successful management and treatment of a multi-risk patients' group.***

Keywords: HIV, Hepatitis C co-infection, c-ART

1. Introduction

Due to shared transmission routes, co-infections with HIV and HCV are very common. Among nearly 40 million infected with HIV worldwide, an estimated 4–5 million (15-30%) are chronically infected with HCV (1). HIV may considerably impact the clinical course and prognosis of HCV infection and vice versa. In the presence of untreated HIV infection, HCV leads to rapid liver fibrosis and decompensation, and increases significantly the risk of liver-related mortality, especially in advancing age (2). Co-infected patients experience more frequent hepatic flares, associated with immune reconstitution during c-ART, or development of resistance to hepatitis treatment (3, 4). Although it remains unclear how HCV affects response to c-ART, a number of studies report a worse immunological response for co-infected individuals (5). The recently introduced into practice direct-acting antiviral agents (DAAs) have dramatically changed the prognosis of HCV infection, allowing a quick and sustained virologic response (SVR) even in case of HIV co-infection and advanced liver disease (6). Against this background, efforts to monitor and manage adequately HCV and HIV co-infected patients have markedly increased.

With 213 new diagnoses, and 2077 registered HIV+ cases in 2014 Bulgaria remains a country with low prevalence of HIV infection: 3.4 %oooo vs. anaverage of 5,9%oooo for EU/EAA (7). Since 2004, owing to an efficient national program for HIV/AIDS prevention, the share of HIV+ patients monitored at specialized departments, and successfully receiving c-ART has been increasing. On the other hand, HIV epidemics in Bulgaria is concentrated among the most vulnerable groups (IDUs, MSM, sex workers, Roma people), with a constant risk of spread among the general population through heterosexual practices (8).

In a previous study, we found that the prevalence of HCV co-infection among the HIV+ patients diagnosed between 2010 and 2014 in Bulgaria was 25.6% (9). This rate was much higher than the estimates for the general Bulgarian population, and fell within the upper range reported for Europe (10, 11). Importantly, high rates of active hepatitis C infection were confirmed by detection of HCV RNA in 78% of the tested individuals (9). HCV co-infection affected mostly high risk groups and persons with multiple risk behavior (9). As none of the co-infected patients received HCV treatment at that time, unique cohorts to evaluate the impact of HCV co-infection on the effects of c-ART emerged.

In the current study we compared the basic demographic and monitoring parameters of HCV co-infected and monoinfected nationwide cohorts of HIV+ patients, diagnosed between 2010 and 2014, and investigated the net effect of active untreated HCV infection on the outcomes of 12- month c-ART.

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2. Patients and Methods

Selection and Description of Participants: All cases with HIV infection documented between 1.01.2010 and 31.12.2014 in Bulgaria were considered retrospectively. Data were retrieved from the National Database for Monitoring and Treatment of HIV-positive patients (HIV+) diagnosed in Bulgaria, containing detailed information on demographics, mode of HIV acquisition, risk behavior, clinical events and co-infections. Data was collected at diagnosis, registration and on a regular 2 to 6-month basis thereafter. The local ethical committees of all participating study sites have approved the study. HIV patients with a positive result for anti-HCV antibodies (anti-HCV) and/or HCV RNA, while HBsAg-negative were defined as co-infected (n=162). HIV patients with negative results for anti-HCV and/or HCV RNA, while HBsAg-negative were defined as mono infected (n=511). Only the co-infected patients with active infection (HCV RNA+) that have completed 12 months of continuous c-ART were included in cohort A (n=52). They were matched with diagnosed during the same period monoinfected patients (n=52) on age, sex, and estimated HIV infection duration (time between diagnosis and c-ART initiation). Similar three-component PI-based or NNRTI-based c-ART regimens were used in cohorts A and B. SVR was defined as suppressed HIV viral load (VL) to undetectable levels (<1.6 $\log_{10}$ copies/ml) 12 months after the start of c-ART. Immune response to c-ART was defined according to the CD4 absolute count (AC) and CD4/CD8 ratio at 12 months, and the change of CD4 AC (□ CD4AC) as compared to baseline.

Technical Information: HIV diagnosis was confirmed at the National Reference Laboratory for HIV, and screening for HCV and HBV infection was carried out at the National Reference Laboratory for Viral Hepatitis, NCIPD. Patients were registered, monitored and treated in the specialized HIV/AIDS departments of the University Hospitals in Sofia, Plovdiv and Varna. ELISA tests were used to detect antibodies to recombinant HCV antigens core, NS3, NS4 and NS5 (HCV Ab version 4.0 DIA.PRO, Milan, Italy) and to HBsAg (HBsAg one 3rd generation DIA.PRO, Milan, Italy). HCV and HIV viral loads were determined with RT-PCR (Abbott m2000rt RealTime™ HIV-1 assay; COBAS TaqMan HCV test, Roche Molecular Systems Branchburg, NJ, USA). CD4AC and CD4/CD8 ratio were determined by multi-parameter flow cytometry (BDMultiTest, TruCount tubes, FACSCanto II) at the National Reference Laboratory for Immunology, NCIPD. All tests were part of the routine laboratory monitoring of the registered HIV+ patients.

Statistics: After assessment for normality, between-group differences were evaluated by the non-parametric Mann-Whitney test (MW) for numerical parameters or chi-square test for categorical data, and Wilcoxon signed-rank test was used when comparing two related groups (GraphPad 6.0).

3. Results

Characteristics of HCV/HIV co-infected patients: Since 2010, extended screening of the newly diagnosed HIV+ cases in Bulgaria for HCV and HBV infection has been performed. Out of 934 HIV+ individuals diagnosed between 2010 and 2014, 794 were tested for the presence of anti-HCV and HBsAg. Of them, 162 were anti-HCVab (+) HBsAg(-) and are further referred to as co-infected; 511 were anti-HCV(-) HBsAg(-), and are further referred to as monoinfected.

While both co-infected and monoinfected patients were predominantly male (83% vs. 80%; p>0.05), co-infected were significantly younger (mean age ± SEM: 29 ± 0.6 vs. 34 ± 0.5 years, p<0.0001), predominantly from the risk group of intravenous drug users (IDUs: 70.4% vs. 2.3%, p < 0.0001) and of Roma origin (40.1% vs. 9.6%, p<0.0001,). At diagnosis, CD4 AC and HIV VL did not differ significantly between co-infected and monoinfected patients (mean ± SEM 352±32 vs. 383±15 cells/µl, and 4.9±0.3 vs. 4.8±0.1 $\log_{10}$HIV RNA copies/ml respectively, p>0.05 for both).However, co-infected patients showed a clear trend for later registration in hospital after diagnosis (mean time between HIV diagnosis and registration± SEM: 133 ± 16 vs. 40 ± 5 days; p<0.0001), and were registered at a more advanced stage of immune deficiency (CD4AC at registration, mean ± SEM: 223 ± 29 vs. 359 ± 36 cells/µl; p<0.01). As a consequence, co-infected patients remained significantly longer without c-ART (mean time between HIV diagnosis and c-ART initiation ± SEM: 373 ± 47 vs. 248 ± 22 days; p<0.01). Finally, co-infected were distinguished by a higher share of dead and lost from follow-up patients (mean% ± SEM: 8 vs. 4; and 32 vs. 22; p<0.05 for both). All characteristics are listed in Table 1.

Impact of HCV co-infection on the effects of c-ART. During the studied period, 36% (59/162) from the newly diagnosed co-infected patients were started on c-ART. Exactly the same was valid for the monoinfected: 36% (185/511). None of the co-infected patients received HCV specific-treatment during the study period**.** In order to assess the net impact of HCV co-infection on the effects of c-ART, and avoid the bias imposed by the later c-ART initiation, we compared the cohorts A and B, matched as described above. Only patients with confirmed active HCV infection were included in cohort A (n=52).

At baseline (just before the start of c-ART) cohorts A and B had similar HIV VL (mean VL± SEM: 4.8 ± 0.2 vs. 5.3 ± 0.2 $\log_{10}$HIV RNA copies/ml, p>0.05); CD4 AC (mean ± SEM: 189 ± 24vs. 231 ± 17cells/µl, p>0.05) and CD4/CD8 index (mean ± SEM: 0.20 ± 0.02 vs. 0.26 ± 0.03, p>0.05).

After 12 months of c-ART, cohort A was characterized by a poorer virological response (mean HIV VL ± SEM: 2.68 ± 0.23vs. 1.54 ± 0.10 Log_{10} HIV RNA copies/ml p<0.01), and significantly higher share of patients without SVR (63% vs. 38%; p<0.0001). Consequently, cohort A had a significantly inferior immune response to c-ART, as described by a lower CD4AC (mean ± SEM: 291 ± 31 vs. 517 ± 36 cells/□ l, p<0.0001), CD4 AC restoration rate (δCD4 mean ± SEM: 110 ± 25 vs. 233 ± 17cells/□ l, p<0.0001), and CD4/CD8 index (mean ± SEM: 0.29 ± 0.04 vs. 0.45 ± 0.03, p<0.0001)**.** All monitoring parameters of cohorts A and B are listed in Table 2.

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4. Discussion

We assessed for the first time the impact of HCV co-infection on the recruitment, monitoring and treatment of HIV+ patients in Bulgaria. This study was evoked by recent data revealing 26% HCV seropositivity among Bulgarian HIV+ patients, and a very high rate of active HCV infections mostly associated with IDU practices.

Our data show that HCV co-infected patients were registered in the specialized HIV/AIDS departments with a significant delay after diagnosis, leading to a more advanced immune deficiency as compared to monoinfected ones. This compromised the possibility for timely start of c-ART. In our hands, at the time of diagnosis HIV VL and immune parameters of co-infected patients were comparable to those of monoinfected, and deteriorated quickly during the following months. This most probably indicates recent HCV and HIV infection, since in IDUs HCV and HIV are often transmitted in parallel, and the effect of HCV seems to be restricted to the first year or so post co-infection (5).Our results underline the importance of large-scale HIV screening combined with HCV screening and early CD4 AC determination, especially in the risk group of IDUs. Reducing the time between diagnosis and registration at hospital, and professional coaching of multi-risk patients during this vulnerable period is essential for successful treatment. An alarming observation of our study was the very low rate of patients with active HCV co-infection subjected to c-ART (51%). It could not be attributed to the older criteria for starting c-ART since most of the co-infected were in advanced stage of immune deficiency already at diagnosis, and all patients have been monitored for at least one year. It was rather due to unsatisfactory preparedness for treatment and poor therapeutic compliance, associated with the multi-risk profile of the group, and confirmed by the high rate of patients lost from follow-up.

The most important observation of our study was asignificant net impact of active HCV infection on the virologic and immunologocal success of c-ART. After 12 months of c-ART and in the absence of HCV-specific therapy, co-infected patients had a significantly inferior viral response and poorer immune response as described by a lower CD4AC restoration rate and persistently low CD4/CD8 ratio. Conflicting data have been published on the effects of untreated HCV co-infection, including studies that report a worse immune response to c-ART (5, 12), and others that have found no such effect (13, 14). Our data support the evidence of negative impact of HCV both on the progress of untreated HIV infection and on the effect of c-ART.

In conclusion, consistent follow-up of HCV-positive cases employing PCR analysis for active infection, timely start on appropriate c-ART, and implementation of DAAs for HCV treatment should be envisaged for the adequate management of this particular patients' group in Bulgaria.

5. Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

Table 1: Characteristics of monoinfected and HCV co-infected HIV+ patients

Parameter	measure	HCV-	HCV+	p
Sample size	n	511	162	/
Male	%	80	83	> 0.05*
Age (mean ± SD SEM)	years	34 ± 0.5	29 ± 0.6	<0.0001*
Risk group: IDUs	%	2.3	70.4	<0.0001*
Roma Origin	%	9.6	40.1	<0.0001*
CD4 AC at diagnosis (mean±SEM)	cells/ml	383 ± 15	352 ± 32	>0.05
HIV VL at diagnosis (mean ±SEM)	Log_{10}HIV RNA copies/ml	4.83 ± 0.1	4.85 ± 0.3	>0.05
Time from diagnosis to registration in hospital (mean±SEM)	days	40 ± 5	133 ± 16	<0.0001**
CD4 AC at registration (mean±SEM)	cells/ml	359 ± 36	223 ± 29	<0.01**
Time from diagnosis to cART initiation (mean±SEM)	days	248 ± 22	373 ± 47	<0.01**
Lost from follow-up	%	22	32	<0.05*
Deaths	%	4	8	<0.05*

p* - probability measured by Chi-square test.
p** - probability measured by Mann-Whitney non-parametric test.
SEM - standard error of the mean

Table 2: Monitoring parameters of cohorts A and B

Parameter	measure	A (HCV+)	B (HCV-)	p
Sample size	n	52	52	/
HIV VL at baseline (mean ± SEM)	Log_{10}HIV RNA copies/ml	4.8 ± 0.2	5.3 ± 0.2	>0.05**
CD4 AC at baseline (mean ± SEM)	cells/ml	189 ± 24	231 ± 17	>0.05**
CD4/CD8 at baseline (mean ± SEM)	/	0.20 ± 0.02	0.26 ± 0.03	>0.05**
HIV VL after 12 months c-ART, mean ± SEM	Log_{10}HIV RNA copies/ml	2.68 ± 0.23	1.54 ± 0.10	<0.01**
Patients without SVR after 12 months c-ART	%	63	38	p<0.0001*
CD4 AC after 12 months c-ART, mean ± SEM	cells/ml	291 ± 31	517 ± 36	<0.0001**
CD4/CD8 after 12 months c-ART, mean ± SEM	/	0.29 ± 0.04	0.45 ± 0.03	<0.0001**
δCD4 AC mean ± SEM	cells/ml	110 ± 25	233 ± 17	<0.0001**

p* - probability measured by Chi-square test.
p** - probability measured by Mann-Whitney non-parametric test.
SEM - standard error of the mean

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