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**EPIDEMIOLOGICAL CHARACTERISTICS AND ACCESS TO END-STAGE LIVER DISEASE CARE FOR HIV-POSITIVE PATIENTS WITH HCV AND/OR HBV COINFECTIONS IN CENTRAL/EASTERN EUROPEAN AND NEIGHBORING COUNTRIES – DATA FROM THE ECEE NETWORK**

**CHARAKTERYSTYKA EPIDEMIOLOGICZNA I DOSTĘP DO OPIEKI W SCHYŁKOWEJ NIEWYDOLNOŚCI WĄTROBY U PACJENTÓW ZAKAŻONYCH HIV WSPÓŁZAKAŻONYCH HCV I/LUB HBV W KRAJACH EUROPY ŚRODKOWEJ/WSCHODNIEJ ORAZ W KRAJACH SĄSIEDNICH - DANE GRUPY ECEE**

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**ABSTRACT**

**OBJECTIVES.** There is currently an urgent need to harmonize hepatitis standards of care for HIV-positive patients across Europe. The HIV epidemic in Central and Eastern Europe has often been driven by injecting drug use, therefore a higher rate of co-infection with HCV and HBV is expected in this region. We have investigated the epidemiological prevalence and treatment availability for end-stage liver disease in HIV/HCV/HBV co-infections in countries represented in the ECEE Network Group.

**METHODS.** The Euroguidelines in Central and Eastern Europe (ECEE) Network Group was initiated in February 2016 to compare standards of care regarding HIV infection in the region. Information about HIV/HCV/HBV co-infections and the availability for end-stage liver disease treatment for HIV-positive patients were collected through on-line surveys. The respondents were ECEE members from 16 countries of the region. The information on co-infection prevalence was sourced from WHO, national HIV programmes, articles published in international journals, single clinic reports, and personal information in ten of the participating countries (62.5%).

**RESULTS.** The HIV/HCV co-infection rate was from 3% to 99%. The range of reported of HIV/HBV co-infection percentages was 2.3% to 40%. HIV/HCV/HBV co-infection ranged from 0% to 9%.

Regarding treatment for end-stage liver disease, liver transplantation was an available option for HIV-positive patients in only three countries (19%).

**CONCLUSION.** Our findings revealed only a limited number of treatment options for the end-stage liver disease in HIV-positive patients for the vast majority of Central and Eastern European countries. There are gaps in epidemiological surveillance in this region. It appears there are many differences in the number of co-infected patients among Central and Eastern European and neighboring countries, but there is no unification of information sources.

**Key words:** *HIV, HCV, HBV, end-stage liver disease*

## STRESZCZENIE

**CELE.** Istnieje pilna potrzeba ujednoczenia standardów opieki nad pacjentami zakażonymi wirusem HIV w całej Europie. Epidemia HIV w Europie Środkowej i Wschodniej często była spowodowana dożylną podażą narkotyków, dlatego w tym regionie stwierdza się większą liczbę koinfekcji z HCV i HBV. Zbadaliśmy epidemiologiczne rozpowszechnienie i dostępność leczenia w końcowym stadium choroby wątroby w koinfekcjach HIV / HCV / HBV w krajach reprezentowanych w Grupie ECEE.

**METODY.** Grupa ECEE (Euroguidelines in Central and Eastern Europe) została stworzona w lutym 2016 roku w celu porównania standardów opieki nad zakażeniem HIV w tym regionie. Informacje na temat koinfekcji HIV / HCV / HBV i dostępności leczenia końcowego stadium choroby wątroby u pacjentów zakażonych wirusem HIV zebrano za pomocą ankiet on-line. Respondentami byli członkowie ECEE z 16 krajów regionu. Źródłem informacji na temat rozpowszechnienia koinfekcji były: WHO, krajowe programy dotyczące HIV, artykuły publikowane w międzynarodowych czasopismach, pojedyncze raporty klinik i informacje personalne w dziesięciu (62,5%) krajach.

**WYNIKI.** Częstość występowania koinfekcji HIV / HCV wynosiła od 3% do 99%. Częstość występowania koinfekcji HIV / HBV wynosiła od 2,3% do 40%. Koinfekcja HCV / HBV i HIV występowała w zakresie od 0% do 9%. Jeśli chodzi o leczenie schyłkowej choroby wątroby, tylko w trzech (19%) krajach transplantacja wątroby była dostępną opcją dla pacjentów zakażonych HIV.

**WNIOSKI.** Nasze wyniki wykazały ograniczoną liczbę opcji leczenia końcowego stadium choroby wątroby u pacjentów zakażonych HIV w większości krajów Europy Środkowej i Wschodniej. W tym regionie występują luki w nadzorze epidemiologicznym. Wydaje się, że istnieje wiele różnic w liczbie pacjentów z koinfekcjami w Europie Środkowej / Wschodniej i krajach sąsiednich, ale nie ma ujednoczonych źródeł informacji.

**Słowa kluczowe:** *HIV, HCV, HBV, schyłkowa niewydolność wątroby*

## INTRODUCTION

HCV and HBV infections are more common in HIV-infected patients than in the general population. It is estimated that HCV infection occurs in 10 million HIV-positive patients, roughly corresponding to one in three HIV-infected patients; whereas HBV infection has been reported as being less common and is found in 3–5 million HIV-positive patients (1).

It is well documented that co-infections of HBV-HIV and HCV-HIV lead to a more rapid progression to liver cirrhosis than HBV or HCV mono-infections (2). Currently, the life expectancy of HIV-infected people is close to that of uninfected people (3). Consequently, we observe disease progression of chronic hepatitis, and especially end-stage liver disease (ESLD), more frequently in these patients (4). ESLD and hepatocellular carcinoma have become leading causes of morbidity and mortality in HBV-HIV, HCV-HIV, and HBV/HCV/HIV-infected patients (5). At the same time it has been well documented that successful treatment of HCV is associated with a decrease in the incidence of liver disease and liver-related death, as well as co-morbidities such as diabetes mellitus (6). However, a worrying findings in a pan-European study has recently been reported, namely, a lower uptake of HCV DAA therapy in Eastern European countries (7).

The HIV epidemic in Central and Eastern Europe has often been driven by injecting drug use, and therefore, a higher rate of co-infection with HCV and HBV is expected and/or registered in this region (8).

Unfortunately, there is no accurate data on the number of HIV-infected patients who are also infected with HBV/HCV in Central and Eastern European Countries. There is currently an urgent need to harmonize hepatitis care for HIV-positive patients across Europe (9).

We have investigated the prevalence of coinfections among HIV infected patients and treatment availability for end-stage liver disease in HIV/HCV/HBV coinfections in countries represented in the ECEE Network Group.

## METHODS

The Euroguidelines in Central and Eastern Europe (ECEE) Network Group was initiated in February 2016 to compare and improve standards of care for HIV infection in the region. Information about HIV/HCV / HBV co-infections and the availability of treatment for the end-stage liver disease in HIV-positive patients was collected through on-line surveys. The respondents were ECEE members from 16 countries from within the region (Bulgaria, Bosnia and Herzegovina, Estonia, Armenia, Greece, Republic of Moldova, Romania, Poland, Slovenia, Croatia, Albania, Hungary, Turkey, Ukraine, Serbia, and Georgia). The online survey included questions about the estimated number of patients infected with HIV/HBV, HIV/HCV, and HIV/ HBV/HCV. The respondents were asked to indicate a specific source for this information. In addition, there was a question about the availability of ESLD treatment (Table 1).

Table 1. On-line survey questions

Tabela 1. Pytania w ankiecie on-line

1. What is your country?
2. What is your current occupation?
3. What is the number of HCV-infected persons in your country? (please provide the source of information and if this number is “diagnosed” or “estimated”).
4. Which group is dominant among HCV-positive persons?
5. Which groups are routinely tested in the public healthcare system for HCV infection (anti-HCV antibodies)?
6. Do you have access to routine HCV RNA testing?
7. Do you have access to routine HCV genotyping?
8. Do you have access to routine HCV resistance testing?
9. Describe the antiviral treatments available for HCV infection in the public healthcare system (free of charge).
10. Do you have DAA drugs available in your country infection in public healthcare (free of charge)?
11. What is the number of HBV infected persons in your country? (please provide the source of information and if this number is “diagnosed” or “estimated”).
12. Which group is dominant among HBV-positive persons?
13. Which groups are routinely tested in the public healthcare system?
14. Do you have access to routine HBV DNA testing?
15. Do you have access to routine HBV genotyping?
16. Which antiviral treatment is available for HBV infections in the public healthcare system?
17. Describe the availability of end-stage liver disease treatment in the public healthcare system.
18. What is the estimated number/percent of HIV-positive patients co-infected with HCV in your country? (please provide the source of information, or write “estimated,” or write “unknown” if it is not possible to estimate)
19. What is the estimated number/percent of HIV-positive patients co-infected with HBV in your country? (please provide the source of information, or write “estimated,” or write “unknown” if it is not possible to estimate)
20. What is the estimated number/percent of HIV-positive patients co-infected with both HCV and HBV in your country? (please provide the source of information, or write “estimated,” or write “unknown” if it is not possible to estimate)

## RESULTS

Sixteen countries participated in the survey, with participants limited to one person from each country. The information on coinfection prevalence was sourced from WHO, national HIV programs, articles published in international peer-reviewed journals, single clinic reports, and personal information in ten of the participating countries (62.5%). The sources of the data were not available for six countries (37.5%), and in these cases personal communication (based on regional/local hospital data) was used instead (Table 2). The results of the survey are shown in Table 2. The HIV/HCV co-infection rate among HIV infected individuals was from 3% to 99%. According to the available data, the highest proportion of HIV/HCV co-infection was reported in Estonia (95–99%). The range of reported HIV/HBV co-infection percentages was from 2.3% to 40% referring to HIV infected patients. The highest percentage of HIV/HBV co-infection was recorded in Romania (10–40%). HIV/HCV/HBV co-infection ranged from 0% to 9%. According to the available data, Romania is the country with the highest seroprevalence of HCV/HBV/HIV co-infection (9%) (Table 2).

Liver transplantation for end-stage liver disease was an available option for HIV-positive patients only in three countries (19%), namely, Bosnia and Herzegovina, Greece, and Poland. At the same time, liver transplantation for HIV-negative patients was possible in nine countries (56%): Bulgaria, Estonia, the Republic of Moldova, Romania, Slovenia, Croatia, Hungary, Turkey, and Serbia. In four countries (25%) – Albania, Ukraine, Armenia, and Georgia – there were no procedures available for ESLD. (Table 3).

## DISCUSSION

In our study, HIV/HCV co-infection rates ranged from 3% to as high as 99% of HIV-positive individuals. The highest reported rate was in Estonia, where the main mode of HIV infection is injecting psychoactive substances use. The highest proportion of HIV/HBV and HIV/HCV/HBV were reported in Romania (10–40% and 9% respectively) in our study. At the same time, our data underlines that access to end-stage liver disease treatment for HIV-positive patients is very poor: only three countries had liver transplantation as an available option for HIV-positive patients.

Table 2. Estimated number (N) or percent (%) of co-infection referred to HIV-positive patients in each country's population. Results from the on-line survey.

Tabela 2. Koinfekcje HIV i wirusowe zapalenie wątroby - wyniki ankiety on-line

Country	HIV/HCV estimated number (N) or percent(%)	HIV/HBV N or %	HIV/HCV/HBV N or %	Source of information
Bulgaria	25.6%	10.4%	3.3%	(38)
Bosnia and Hercegovina	6%	4%	none	Personal communication (Velida Mulabdic) Unpublished data from the Clinic for Infectious Disease in Sarajevo.
Estonia	95–99%	4–5%	4.5%	(39)
Armenia	13.9%	2.3%	0.24%	Personal communication (Tatevik Balayan, National Center for Disease Control and Prevention, Yerevan, Armenia).
Greece	12.8%	3–6%	0.09%	(4, 40)
Republic of Moldova	16.5%	6.4%	5%	(41)
Romania	20%	10–40%	9%	(42)
Poland	33%	15%	7%	Personal communication (Karolina Pyziak-Kowalska; Hospital for Infectious Diseases, Warsaw).
Slovenia	5.7%	4%	unknown	(43)
Croatia	39 (N)	4%	<1%	Personal communication (Josip Begovac, University of Zagreb School of Medicine, University Hospital of Infectious Diseases, Zagreb, Croatia).
Albania	3–5%	17–20%	1.5–2%	Infectious Disease Service, University Hospital center of Tirana (Arjan Harxi).
Hungary	100 (N) per 2,000 HIV-positive	70 (N) per 2,000 HIV-positive	10 (N) per 2,000 HIV-positive	National HIV Center (Botond Lakatos, Saint Laszlo Hospital National Center of HIV, Semmelweis University Faculty of Infectious Diseases, Budapest, Hungary).
Turkey	2,000 (N)	6,000 (N)	1,000 (N)	Personal communication (Tansu Yamazhan, Ege University faculty of Medicine Department of Infectious Diseases and Clinical Microbiology Bornova Izmir, Turkey).
Ukraine	unknown	unknown	unknown	Personal communication (Marta Vasylyev, Lviv Regional AIDS Center, Lviv, Ukraine).
Serbia	25%	4.5%	1.7%	PhD student of Dr. Jovan Ranin, Infectiologist, HIV clinician.
Georgia	34%	unknown	1.9%	Personal communication (Nikoloz Chkhartishili, Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia).

Our results show huge disparities in the epidemic across a relatively small geographical region, and underlines the need for an individualized approach to HCV elimination. Our data correlates well with estimates from global reports. In a systematic review and meta-analysis published in 2016, Platt et al. analyzed the general prevalence of HIV/HCV coinfections among HIV-positive patients, and obtained a result of 6.2% (10). They found a total of

around 2,278,400 HIV/HCV co-infections worldwide. Of these people 1,362,700 were injecting drug users (IDU), which means that IDU patients had the highest risk of HIV/HCV co-infection. Vickerman et al published data about the 90% prevalence of HIV/HCV co-infection among HIV-infected IDUs across 43 countries (11). Soriano et al published data about the HIV/HCV epidemic in Russia and Ukraine (12). The prevalence of co-infection in these countries was 70%,

and was connected with the most common route of infection – injecting drug use. In contrast, in Western Europe countries, the prevalence of HIV/HCV co-infection is estimated to be 10–15% (13). This is due to the different routes of HIV/HCV transmission. In Western European countries men who have sex with men (MSM) is the dominant population having HIV/HCV-infected individuals (13).

Table 3. Availability of end-stage liver disease treatment for patients in Central and Eastern Europe

Tabela 3. Dostępność leczenia schyłkowej choroby wątroby u pacjentów z HIV w Europie Środkowej i Wschodniej

Country	Liver transplantation for HIV-negative	Liver transplantation for HIV-positive
Bulgaria	Yes	No
Bosnia and Hercegovina	Yes	Yes
Estonia	Yes	No
Armenia	No	No
Greece	Yes	Yes
Republic of Moldova	Yes	No
Romania	Yes	No
Poland	Yes	Yes
Slovenia	Yes	No
Croatia	Yes	No
Albania	No	No
Hungary	Yes	No
Turkey	Yes	No
Ukraine	No	No
Serbia	Yes	No
Georgia	No	No

Regional data may differ significantly from global data due to epidemiological differences in specific populations and the most common routes of HIV infection. In the USA, Soriano et al (14) estimated that about 30% of HIV-positive patients had HCV coinfections. On the other hand, two regional meta-analyses in South Africa (15, 16) documented that HIV/HCV co-infections were 7% and 5.7% among HIV-positive individuals. Numbers of HIV/HCV-co-infected patients were estimated to be higher in China with the overall prevalence being 41.8% (17). It is probable that the number of HIV/HCV co-infections will decrease in Central and Eastern European countries due to the wide availability of antiviral drugs (18).

The range of reported HIV/HBV co-infection percentages was from 2.3% to 40% in our study. It is estimated that globally, 10% of the HIV population is HBV-co-infected (19). The prevalence of HBV varies depending on the geographical region (20). In the endemic regions of Asia most HBV infections are acquired by children under five years of age, which results in chronic infections. Feng et al published Chinese data in which the prevalence of HBV and HIV co-infection was 13.85% (21). Similar results were found in Africa (22). On the other hand, in Europe and United States the majority of HBV/HIV co-infections occur in the MSM population (23).

In our study, HIV/HCV/HBV co-infection ranged from 0% to 9%. Owing to shared routes of transmission, HIV/HCV/HBV triple infections usually occur in IDUs (24). However, the prevalence of HIV/HCV/ HBV infections is low as evidenced by the results in individual scientific publications. In USA, HBV/HCV co-infections were detected in 1.58% of HIV-positive patients (25), but in a Spanish cohort the prevalence of multiple hepatitis was 4.7% (26). In Chinese prevalence studies, HIV/HCV/HBV triple infections were estimated to be 6.9%, 6.0%, and 8.5% in plasma donors, blood recipients, and IDUs respectively (27).

Non-AIDS-related conditions account for an increasing proportion of HIV-infected patients' death, with liver and kidney failure causing death in an estimated 10% of patients (28). Transplantation as a treatment option for HIV-positive patients emerged in 1990s, and nowadays is available in many Western countries for these patients. A report from the University of California, San Francisco in 2003, described a cohort study of 14 HIV-positive patients who received either a kidney or liver transplant (29). For the four liver transplant recipients, patient and graft survival was 75% at 380 days. The single death in the liver transplant group was caused by recurrence of HCV. Over the last years, several studies have confirmed that HIV-positive recipients have liver graft and patient survival rates similar to HIV-negative recipients, with the exception of recipients who are co-infected with HIV and HCV (30-32). But even in co-infected patients, especially taking into consideration the lack of other treatment options, results seem to justify referring these patients for transplantation. Additionally, with increasing expertise and new treatment options we are now able to identify several modifiable donor/recipient risk factors that could be changed in order to improve survival in HIV/HCV-co-infected patients (32).

Our findings revealed a lack of treatment options for ESLD in HIV-positive patients for the vast majority of Central and Eastern European countries. Among the sixteen countries only one in five had liver

transplantation as an available option for HIV-positive patients as a treatment for end-stage liver disease. This may underestimate access to transplantation, as, at least in some countries, despite the lack of a systemic solution, HIV-positive patients can receive solid organ transplants (33). While in some regions this might reflect poor access to transplantation medicine in general (34). Another possible limitation on liver transplantation might be low numbers of donors.

As mentioned above patient and graft survival is comparable in HIV-negative and HIV-positive recipients. It seems that nowadays there is no reason to deny access to liver transplantation for HIV-infected individuals who meet the established criteria (32). Still, there is the serious and worldwide issue of organ shortage for transplantation. In the past, using organs from HIV-positive donors has been avoided because of concerns about HIV superinfection and transmitted drug resistance; although, in clinical studies the survival rates are similar to those of HIV-positive recipients who obtain organs from HIV-negative and HIV-positive donors (32, 35, 36). In the United States, the use of HIV-positive donor organs was legalized in 2013, but only in the setting of an approved research protocol (37). This may prove helpful in the future, especially in countries with high numbers of infected individuals, although such opportunities have still not been well explored in Europe. All these factors which limit access to transplantation, as well as the inferior survival of HCV-co-infected patients, indicate that resource limited countries should be targeted with programs for wide access to hepatitis treatment in order to prevent mortality.

Despite good survival rates, treatment of HIV-positive transplant recipients remains an ongoing challenge and requires a highly experienced and multidisciplinary team. Some recommendations state: “avoid liver transplantation in centers with a low volume of liver transplantation in HIV-infected patients and no well-organized multidisciplinary team” (32). This may be a serious obstacle for centers with small numbers of transplants per year. In such a setting access to transplantation may be restricted for HIV-positive patients.

Antirejection treatment after transplantation requires a high level of compliance. When the proportion of injecting drug users among the HIV-infected population is high, as it is in some Eastern European Countries, this may raise serious concerns about non-compliance and a resulting increase in risk of acute rejection or other complications after transplantation procedures. Also, the careful selection of potential recipients in terms of psychological assessment seems to be crucial for success.

There are some important limitations to be discussed regarding the study. First of all this is an on-line survey based study in which we have pre-selected respondents based on our best knowledge of their expertise and up-to-date acquaintance with epidemiological and clinical data from the country. Second, the sources of information on coinfection prevalence varied from personal communication to detailed epidemiological surveillance, thus the weight of the data presented varies significantly across countries.

Irrespective of the above limitations our work shows that the lack of standardized epidemiological data collection on co-infections is a serious obstacle to providing targeted national programs for eliminating HCV and HBV infection. In addition, we identified an urgent need to improve access to end-stage liver disease treatment in the Central and Eastern European region and neighboring countries, both for HIV-negative and HIV-positive patients.

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