The Outcome of Coronavirus Disease 2019 among People Living with HIV in European Union versus Non-European Union Countries

Keywords
HIV, COVID-19, Europen Union Countries, nonEuropean Union Countries

Abstract
Introduction
The Central and Eastern Europe (CEE) region differs in access to HIV and co-infections care and treatment. The aim of the study was to analyze the relation between the severity of the COVID-19 disease and HIV specific factors in the European Union (EU) Countries and in non-European Union (non-EU) Countries.

Material and methods
The study was conducted between November 2020 and May 2021. Euroguidelines in Central and Eastern Europe (ECEE) Network Group was collecting observational data on HIV-positive patients diagnosed with COVID-19. In total, 16 countries from CEE (Poland, Czech Republic, Ukraine, Croatia, Turkey, Romania, Belarus, Estonia, Lithuania, Greece, Georgia, Albania, Hungary, Serbia, Bosnia and Herzegovina, and Bulgaria) submitted data on HIV-positive patients using an electronic case report form (eCRF). Chi-Square test was used for group comparisons.

Results
In total 557 patients were included into the analyses: 361 from EU and 196 from non-EU countries. Access to remdesivir was 1.5% in non-EU countries vs 3.9% in EU-countries (p= 0.1952) . Symptoms of COVID-19 occurred more often in non-EU countries (93.3%) vs non-EU countries (83.6%) [p=0.0009], as well as hospitalization 32.8% vs. 20.8% respectively [0.0027]. Death/ICU was 4.8% in non-EU countries vs 3.4% in EU-countries (p=0.4877). In total 18 (3.23%) patients found out about HIV diagnosis during COVID-19, which was comparable in two groups (11 [3.0%] in UE countries vs. 7 [3.6%] in non-UE countries; p=0.8029).

Conclusions
Patients from non- EU countries were more likely to be COVID-19 symptomatic and hospitalized. Access to antiviral therapy for SARS-CoV-2 was very low for all CEE countries.

The Outcome of Coronavirus Disease 2019 among People Living with HIV in European Union versus Non-European Union Countries

Abstract:

Introduction: The Central and Eastern Europe (CEE) region differs significantly in access to Human Immunodeficiency Virus (HIV) and co-infections care and treatment. A worse access to HIV care during pandemic as well as poor access to modern combinated antiretroviral treatment (cART) and newest Coronavirus Disease 2019 (COVID-19) treatment strategies could have a negative impact on countries depending on their EUROPEAN UNION (EU) membership. The aim of the study was to analyze the relation between the severity of the COVID-19 disease and HIV specific factors in the European Union Countries and in non-European Union Countries.

Methods: The study was conducted between November 2020 and May 2021. Euroguidelines in Central and Eastern Europe (ECEE) Network Group was collecting observational data on HIV-positive patients diagnosed with COVID-19. In total, 16 countries from CEE (Poland, Czech Republic, Ukraine, Croatia, Turkey, Romania, Belarus, Estonia, Lithuania, Greece, Georgia, Albania, Hungary, Serbia, Bosnia and Herzegovina, and Bulgaria) submitted data on HIV-positive patients using an electronic case report form (eCRF). Chi-Square test was used for group comparisons.

Results: In total 557 patients were included into the analyses: 361 from EUROPEAN UNION and 196 from non-EUROPEAN UNION (non-EU) countries. In general, 426 (76.5%) patients were males, median age in years was 43.4 [IQR:6-86] median time since HIV diagnosis in years was 9.13 [0-33], median CD4 count before COVID-19 diagnosis was 635 [2-2099] copies/mm3 and 474 (85%) patients had viral load <50 copies/ml before COVID-19 diagnosis. In total 21 (3.9%) of patients died or have been treated in intensive care units (ICU), 17 (3.0%) received remdesivir. Access to remdesivir was 1.5% in non-EU countries vs 3.9% in EU-countries (p= 0.1952) . Symptoms of COVID-19 occurred more often in non-EU countries (93.3%) vs non-EU countries (83.6%) [p=0.0009], as well as hospitalization 32.8% vs. 20.8% respectively [0.0027]. Death/ICU was 4.8% in non-EU countries vs 3.4% in EU-countries (p=0.4877). In total 18 (3.23%) patients found out about HIV diagnosis during COVID-19, which was comparable in two groups (11 [3.0%] in UE countries vs. 7 [3.6%] in non-UE countries; p=0.8029).

Conclusions: Patients from non- European Union countries were less likely to have HIV viral load <50 copies/ml and CD4 count above 350 cells/mm3, as compared to patients from European Union countries. They were also more likely to be COVID-19 symptomatic and hospitalized. However, it did not translate into difference in death/ICU. Access to antiviral therapy for SARS-CoV-2 was very low for all CEE countries.

Keywords: HIV; COVID-19; Central and Eastern Europe; European Union; COVID-19 WHO stages

*HIV – human immunodeficiency virus

*COVID-19 - Coronavirus Disease 2019

*COVID-19 WHO stages - Coronavirus Disease 2019 World Health Organization stages

1. Introduction

Since Coronavirus Disease 2019 (COVID-19) pandemic outbreak, millions of people have lost their lives and over half a billion have fallen ill across the world (1). Some of the risk factors for severe COVID-19 (older age, cardiovasculary disease (CVD), pulmonary disease) are more prevalent in people living with HIV (PLWH) than those without HIV (2-4). Because of that, although HIV itself may not predispose to markedly more severe COVID-19 outcomes, we could expect that population of people living with HIV could be more affected by COVID-19 than general population.

The Central and Eastern Europe (CEE) region differs significantly in access to HIV and co-infections care and treatment. In the recent studies from the region initiation of ART(antiretroviral treatment) regardless of the CD4+ T cell count was significantly more common among high-income countries than among upper-middle-income and lower-middle-income countries (100% vs. 27.3% and 0%, respectively; p=0.001) .The treatment for end-stage liver disease, liver transplantation was an available option for HIV-positive patients in only three CEE countries (19%) (5, 6). Moreover, the Joint United Nations Programme on HIV and AIDS (UNAIDS) reports that between 2010 and 2018, there was a 30% increase in HIV infections in Eastern Europe (7). A worse access to HIV care during COVID-19 pandemic as well as poor access to modern combinated antiretroviral therapy (cART) and newest COVID-19 treatment strategies could have a negative impact on the future course of COVID-19 among

countries depending on their EUROPEAN UNION membership (8). On the other hand, maybe thanks to the COVID-19 pandemic, governments pay more attention to the importance of public health and greater control of the HIV epidemic is possible in the region of Central and Eastern European Countries (9).

In our study we analyzed the relation between the severity of the COVID-19 disease and HIV specific factors in the European Union Countries and in non-European Union Countries. At the beginning of COVID-19 pandemic it was not known how COVID-19 outcomes in PLWH would be. The standards of care for COVID-19 patients have changed, especially at the beginning, during the first wave and PLWH group is a special group of patients. To our knowledge, there was not such a study of PLWH patients with COVID-19 in our region. We also compared similarities and differences between EU and non-EU countries and the access to antiviral therapy for SARS-CoV-2 in the region.

2. Methods

The Euroguidelines in Central and Eastern Europe (ECEE) Network Group was established in February 2016 to promote standards of care for HIV and viral hepatitis infections in the region. The group includes experts in the field of infectious diseases from 26 countries in the region, who are also professionals actively involved in the care of infectious diseases (10).

The study was conducted between November 2020 and May 2021. ECEE Network Group members were collecting observational data on people living with HIV diagnosed with COVID-19. In total, 16 countries from Central and Eastern European submitted data on HIV-positive patients, the data was collected for research, using an electronic case report form (eCRF) built on the SurveyMonkey® platform and were collected retrospectively. Data was provided by medical doctor taking care for HIV patients. Data was collected from Poland, Czech Republic, Ukraine, Croatia, Turkey, Romania, Belarus, Estonia, Lithuania, Greece, Georgia, Albania, Hungary, Serbia, Bosnia and Herzegovina, and Bulgaria. Clinical data included demographics, lifestyle, HIV viral load (VL), Lymphocyte CD4+ cell count, history of antiretroviral treatment, and COVID-19 clinical course. Non-AIDS related comorbidities such as cardiovascular, respiratory disease, kidney disease, diabetes, and malignancy were also included. All patients were adults and under the care of specialized HIV outpatient clinics.

The current analyses included people living with HIV diagnosed with COVID-19 comparing Europenian Union (Bulgaria, Croatia, Czech Republic, Estonia, Greece, Hungary, Lithuania, Poland, Romania, Serbia) vs non-Europenian Union countries (countries that do not currently

have member status of the European Union), (Albania, Belarus, Bosnia and Herzegovina, Georgia, Turkey, Ukraine).

In the statistical analyses Chi-Square test was used for group comparisons, the p value below 0.05 was accepted as significant. All analyses were performed with SAS software version 9.4.

The design of this work conforms to the standards currently applied in the Medical University of Warsaw's Bioethics Committee. Approval number: AKBE/155/2020. The Bioethics Committee decision was received on 16th September 2020 .

3. Results

In total 557 patients were included into the analyses. In the study eleven HIV centres from ten European Union countries (Bulgaria, Croatia, Czech Republic, Estonia, Greece, Hungary, Lithuania, Poland, Romania, Serbia) took part in the study. Among non-European Union seven HIV centres from six countries (Albania, Belarus, Bosnia and Herzegovina, Georgia, Turkey, Ukraine) declared their participation.

The baseline characteristics of people living with HIV included into the study in European Union Countries and Non-European Union Countries are presented in Table 1.

Table 1. Baseline characteristics of people living with HIV included into the study in European Union Countries and Non-European Union Countries.

Characteristic	European Union Countries N=361	Non-European Union Countries N=196	Total N=557	p-value
Sex at birth N (%)				<0.00001
male	298 (82.5)	128 (65.3)	426 (76.5)	
female	63 (17.5)	68 (34.7)	131 (23.5)	
Age in years, median [IQR*]	42.6 [19-83]	44.81 [19-86]	43.4 [19-86]	0.6624

BMI** in kg/m^2, median [IQR]	25.3 [14.7-60.1]	25.49 [19-44.1]	25.37 [13.5-60.1]	0.4275
Time since HIV diagnosis in years median [IQR*]	9.73 [0-33]	8.01 [0.5-24]	9.13 [0-33]	0.3128
CD4 count before COVID-19 diagnosis median [IQR] copies/ml	659.78 [11-2093]	588.58 [11-1656]	635.03 [2-2093]	0.4268
CD4 count after COVID-19 diagnosis median [IQR] copies/ml	630.15 [2-2099]	534.75 [7-1414]	595.93 [2-2099]	0.4467

*IQR - interquartile range **BMI - body mass index.

Patients from non- European Union countries were less likely to have HIV viral load <50 copies/ml and CD4 count above 350 cells/mm3, as compared to patients from European Union countries. They were also more likely to be COVID-19 symptomatic and hospitalized. Access to antiviral therapy for SARS-CoV-2 was very low for all CEE countries. (Table 2).

Table 2. Factors associated with HIV, COVID-19, comorbidities and socio-economic situation among people living with HIV in European Union Countries and Non-European Union Countries.

Characteristic	**European Union Countries N (%)**	**Non-European Union Countries N (%)**	**Total N (%)**	**p value**
Factors associated with HIV				
The last viral load				0.0135
<50 copies/ml	316 (87.8)	158 (79.0)	474 (85)	
>=50 copies/ml	45 (12.5)	40 (20.4)	85 (15.2)	
The last CD4 count				0.0170

>350 cells/ul	296 (82.0)	142 (75.2)	438 (78.6)	
=<350 cells/ul	66 (18.3)	53 (27.0)	119 (21.36	
Route of infection				<0.0001
heterosexual	80 (22.1)	97 (49.7)	117(31.8)	
IVDU***	46 (12.7)	39 (20.0)	85 (15.3)	
MSM****	219 (60.5)	48 (24.6)	267 (47.9)	
unknown	11 (3.0)	11 (5.6)	22 (3.95)	
other	6 (1.08)	0 (0.0)	6 (1.08)	
ARV	343 (94.7)	181 (92.8)	524 (94)	0.3537
HIV diagnosis during COVID-19	11 (3.0)	7 (3.6)	18 (3.23)	0.8029
Habits				
Using of psychoactive substances				0.0448
In the past	94 (25.9)	39 (20.0)	133 (23.9)	
never	228 (62.9)	141 (72.3)	369 (66.2)	
now	32 (8.8)	15 (7.7)	47 (8.4)	
unknown	8 (2.2)	0 (0)	8 (1.4)	
Smoking				0.0003
In the past	69 (19.0)	65 (33.3)	134 (24.06)	
never	164 (45.3)	71 (36.4)	235 (42.2)	
now	114 (31.5)	58 (29.7)	172 (30.9)	
unknown	15 (4.1)	1 (0.5)	16 (2.9)	

Comorbidities				
Comorbidity	105 (29.0)	53 (27.0)	158 (28.4)	0.6939
Viral coinfections (HBV and/or HCV)	44 (13.0)	31 (15.9)	75 (14.1)	0.0933
Socio-economic situation				
Current employed	273 (75.4)	136 (69.7)	409 (73.4)	0.1597
COVID-19 treatment				
Remdesivir	14 (3.9)	3 (1.5)	17 (3)	0.1952
% Patients with severe COVID-19 on Remdesivir	18.6	4.8	12.3	0.0275
Factors associated with COVID-19				
Death/ICU	12 (3.4)	9 (4.8)	21 (3.9)	0.4877
Hospitalization	75 (20.8)	63 (32.8)	138(25)	0.0027
COVID-19 diagnosis				0.2621
PCR SARS CoV-2	312 (86.4)	175 (89.3)	487 (87.59)	
radiology	1 (0.3)	2 (1.0)	3 (0.54)	
serology	40 (11.1)	14 (71.5)	54 (9.71)	
symptoms	9 (2.5)	3 (1.5)	12 (2.16)	
Symptoms at baseline	302 (83.6)	182 (93.3)	484 (86.89)	0.0009

*** IVDU - intravenous drug users **** MSM – men who have sex with men. *ICU – Intensive Care Unit

Comorbidities among people living with HIV diagnosed with COVID-19 in European Union Countries and Non-European Union Countries are presented in Table 3.

Table 3. Comorbidities among people living with HIV diagnosed with COVID-19 in European Union Countries and Non-European Union Countries.

Comorbidities	UE countries (Total participants 361)	Non-UE countries (Total participants 196)	Total participants 557	p-value
Cardiovascular diseases	64 (17%)	32 (16%)	96 (17%)	0.7247
Respiratory diseases	23 (6.3%)	7 (3.5%)	30 (5.3%)	0.1835
Kidney diseases	11 (3%)	7 (3.5%)	18 (3.2%)	0.7464
Malignancies	13 (3.6%)	5 (2.5%)	18 (3.2%)	0.5163
Diabetes	19 (5.2%)	10 (5.1%)	29 (5.2%)	0.9381
Liver cirrhosis	5 (1.3%)	3 (1.5%)	8 (1.4%)	0.8919
HCV	30 (8.3%)	19 (9.6%)	49 (8.7%)	0.6148
HBV	12 (3.3%)	7 (3.5%)	19 (3.4%)	0.8820
HCV+HBV	7 (1.9%)	0 (0%)	7 (1.2)	0.1812
Other	19 (5.2%)	10 (5.1%)	29 (5.2%)	0.9341

In general, 398 (71.1%) people living with HIV diagnosed with COVID-19 didn't require hospitalization, in this group of patients 271 (48.8%) were from European Union Countries. Among patients, who were hospitalized, requiring normal oxygen supplementation, 24 (4.3%) were from European Union Countries and 13 (2.3%) were from non-European Union Countries. Only one patient, from European Union Countries, was hospitalized, with invasive mechanical ventilation or ECMO, (Figure).

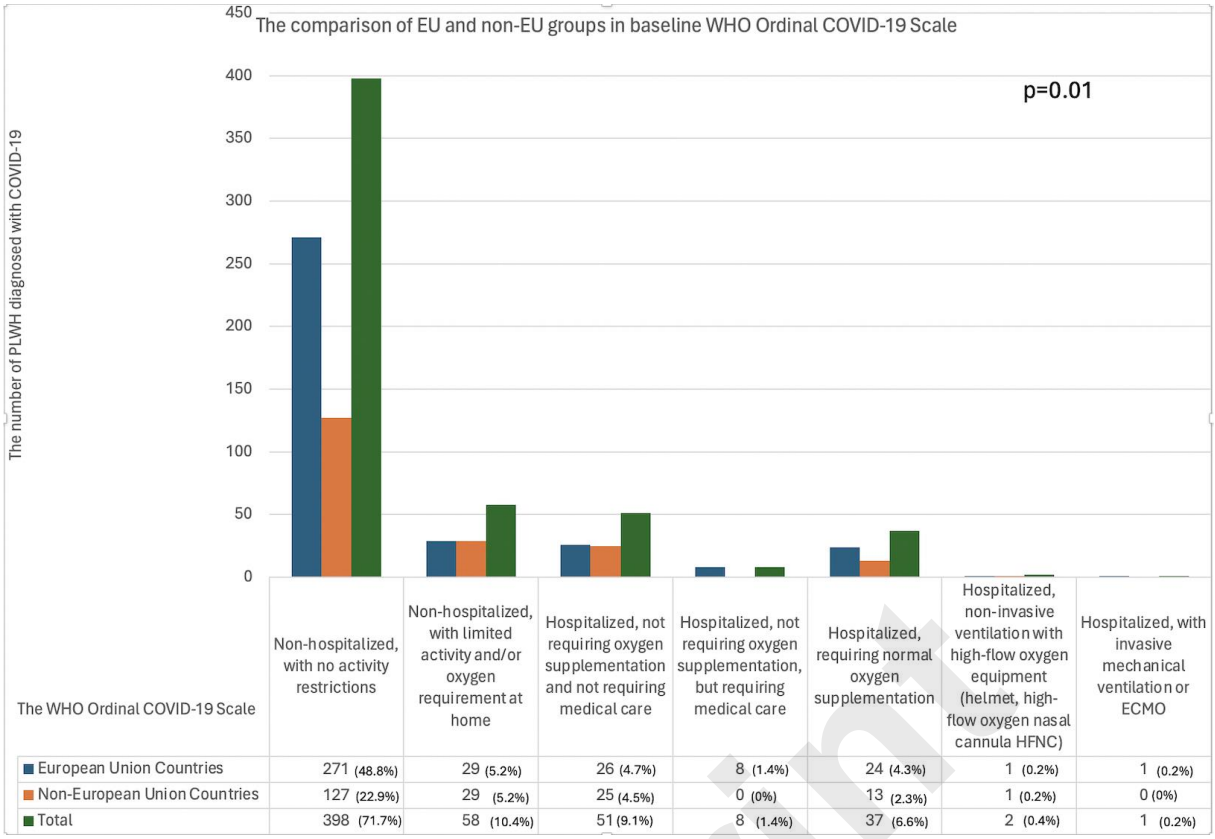

Figure 1. The comparison of WHO Ordinal COVID-19 Scale at baseline between European Union and non-European Union countries

Univarinate regression model reveald that patients from non-UE region had a higher odds of death and/or ICU admission, however without statistical significance (OR=1.404, ;95CI 0,581-3,396).

4. Discussion

The results of the current study suggest that, based on studied countries, differences exist in caring for people living with HIV and COVID-19 between -European Union and non-European Union countries of Central and Eastern Europe. These reflects the observed discrepancies in access to HIV care, as well as higher proportion and diversity of hard-to-reach populations (11).

Another observation is that patients in our study were also more likely to be COVID-19 symptomatic and hospitalized comparing to the general population. At the beginning of COVID-19 pandemic there was concern that people living with HIV, would suffer from more severe COVID-19 than general population due to immunodeficiency. By depleting CD4 cells, HIV causes immunodepression and at the same time reducing availability of the organism to defend against viral infections including COVID-19, but also bacterial, parasitic, and fungal infections (12). The more severe immunodepression and the patient is not on ARV, the greater vulnerability to infections is observed (13). However, the way individuals experience infections depend on many factors, including genetical predisposal and co-morbidities. In people living with HIV the latter being the most worrying factor, as immune activation linked to minimal HIV replication, even in people of fully suppressive antiretroviral therapy, results in higher prevalence and earlier presentation of different co-morbidities, especially cardiovascular diseases and diabetes (14). Moreover, people living with HIV are more likely to smoke, which is a factor predisposing to respiratory infections (15). This may indicate that due to the worse course of the disease, these patients were hospitalized, and HIV was detected at the same time. Initially, case series and small cohorts showed no impact of HIV. Population-based cohort in Wuhan, China, study found lower incidence of COVID-19 among people living with HIV compared to the general population early in the pandemic (0.38%, 95% confidence interval (CI): 0.24–0.53% vs. 0.45%, 95% CI: 0.45–0.46%) (16)**.** Throughout the pandemic, lower or similar incidences of COVID-19 among people living with HIV were observed comparing to general population in large, population-based studies. In Nomah et al. study it was not found that in Catalonian population, any significant differences were seen between people living with HIV diagnosed with COVID-19 comparing to the the general population in terms of hospitalization (13.75% vs. 14.97%, $p = 0.174$) and Intensive Units Care admission (0.93% vs. 1.66%, $p = 0.059$). Moreover, lower mortality rate among people living with HIV diagnosed

with COVID-19 was observed compared to the general population (1.74% vs 3.64%, $p = 0.002$) (17). The findings from these studies may have resulted from greater social distancing, especially during early pandemic period, among people living with HIV, because of mentioned concerns (18).

On the other hand, in Danwang et al. study, people living with HIV had an increased risk of hospitalization for COVID-19 than general population. In this systematic review and meta-analysis, in which included 44 studies were included the pooled prevalence of HIV among COVID-19 patients was 26.9%. Regarding to the study people living with HIV diagnosed with COVID-19 were more likely to be admitted to hospital (OR: 1.49; 95% CI 1.01-2.21, 6 studies) compared to individuals without HIV. What is more, HIV was associated with an increased risk of death (hazard ratio: 1.76, 95% CI 1.31-2.35), (19). Moreover, larger cohorts from United Kingdom and United States of America showed higher mortality of people living with HIV diagnosed with COVID-19. In UK population people living with HIV had higher risk of death caused by COVID-19 than people without HIV after adjusting for age and sex: hazard ratio (HR) 2·90 (95% CI 1·96-4·30; p<0·0001) and in United States of America people living with HIV diagnosed with COVID-19 were hospitalized more than persons without HIV, per population (sRR, 1.38 [95% CI, 1.29-1.47]); moreover, mortality among people living with HIV diagnosed with COVID-19 was observed per population (sRR, 1.23 [95% CI, 1.07-1.40]) and among those diagnosed (sRR, 1.30 [95% CI, 1.13-1.48]). Hospitalization risk increased with disease progression to HIV stage 2 and stage 3 comparing to stage 1 (20, 21). Significant limitation for some of these studies was no access to HIV specific data, such as HIV viral load and Cd4 lymphocyte count. Among the studies including these factors some showed that lower current/nadir CD4 and/or detectable viral load were associated with worse outcomes, others did not find such correlation (2).

Regarding the outcome of COVID-19 the results of published studies are rather contradictory. In some studies, it was found that mortality and composite outcome (ICU admission, invasive ventilation, or death) were lower among people living with HIV (22, 23). In the other studies, it was observed that people living with HIV have a higher risk of COVID-19 diagnosis, but similar outcomes to general population. Regarding Tang et al. study relative to people without HIV, people living with HIV did not have an increased rate of COVID-19 hospitalization [adjusted incidence rate ratio (aIRR) = 0.5, 95% CI: 0.1-1.4], they also did not have a different rate of ICU admission (aIRR = 1.08, 95% CI: 0.31-3.80) or of in-hospital death

(aIRR = 0.92, 95% CI: 0.08-10.94) (24). Even in systematic reviews and meta-analyses we could find different findings. Dzinamarira et al. study did not link HIV with increased COVID-19 mortality. In this review, which included 16 studies, among people living with HIV diagnosed with COVID-19, the mortality rate due to COVID-19 was 7.97%, and among the COVID-19 patients without HIV infection, the mortality rate due to COVID-19 was 0.69%. However, in the random effects model, they found no statistically significant relative risk of mortality in people living with HIV diagnosed with COVID-19 (RR 1.07, 95% CI 0.86-1.32), (25). On the other hand, Wang et al. showed that people living with HIV are at increased risk of COVID-19 related mortality. In this systematic review and meta-analyses 32 studies were included. According to the results of the study people living with HIV had comparable risk of COVID-19 (adjusted RR=1.07, 95% CI: 0.53-2.16, I^2 = 96%) and risk of developing severe COVID-19 symptoms (aRR=1.06, 95% CI: 0.97-1.16, I^2 = 75%). Moreover, people living with HIV diagnosed with COVID-19, were found to have an increased risk of mortality compared with people without HIV (aRR=1.30, 95% CI: 1.09-1.56, I^2 = 76%), (26). In our study 398 (71.1%) people living with HIV diagnosed with COVID-19 didn't require hospitalization, in this group of patients 271 (48,8%) were from European Union Countries.

In Central and Eastern Europe in retrospective analysis which included all confirmed COVID-19 cases from twelve countries between March 11 and June 26, 2020, most HIV-positive patients had full clinical recovery (91%). In the mentioned study 34 cases of people living with HIV diagnosed with COVID-19 were observed mostly as mild disease (27). In the other study from this region HIV viral suppression and immunological status were not associated with the course of COVID-19 disease (28). In general, Central and Eastern European region differs in access to HIV and co-infections care and treatment (5,6). In our current analysis the access to remdesivir was comparable for both groups of countries, but very modest in general for the Central and Eastern Europe ranging from 1.5% to 3.9%. In Grundeis rt al. study remdesivir has little or no effect on all-cause mortality or in-hospital mortality of individuals with moderate to severe COVID-19 in general population (29). However, is was shown on polish population that certain risk groups, especially immunocompromised patients would benefit from remdesivir therapy (30). Only a few immunocompromised patients participated in the PINETREE trial regarding early 3-day regimen of remdesivir used in high-risk individuals to prevent COVID-19 progression. During this study investigators did not disclose if any patients with HIV participated and the observed that remdesivir is not associated with significant adverse events aside from transient increases in transaminase levels nor with any important drug–drug interactions (31). In Lakatos et al. study from the Central and Eastern

European region on HIV-positive persons receiving COVID-19-specific treatment, it was found that potential drug-drug interactions were common. In the study 62 drug-drug interactions episodes were identified in 58 people living with HIV diagnosed with COVID-19 (11.8% of the total cohort and 41.9% of the COVID-19-specific treatment group). The use of boosted protease inhibitors and elvitegravir accounted for 43 drug-drug interactions (29%), whereas nonnucleoside reverse transcriptase inhibitors were responsible for 14 drug-drug interactions (9.5%).Although low-dose steroids are mainly used for COVID-19 treatment, co-medication with boosted antiretrovirals seems to have the most frequent potential for drug-drug interactions (32).

Another important aspect in caring for people living with HIV is access to doctors' visits and antiretroviral drugs disposal. As we know in the beginning of pandemic majority of healthcare facilities were closed, and only centers treating COVID-19 were admitting patients. Many people with chronic diseases experiences disruption in care, followed by increased morbidity and even mortality (8). Fortunately, this was not the case for HIV field. As presented by Kowalska et al. although infectious diseases doctors and nurses working in HIV centers were at the same time involved in COVID-19 care none of 19 Central and Eastern European countries reported HIV clinic closures. In one third countries HIV clinics were operating normally, but in remaining countries physicians were sharing HIV and COVID-19 care duties. None of the countries experienced shortage of ART.

Such sustained access to care was also followed by access to SARS-CoV-2 testing, which in turn could result in increased detectability among people living with HIV. Also, people with certain conditions though to be more vulnerable towards infection or at higher risk of unfavorable outcome were more likely to be tested. As recently published by EuroSIDA study group people from Northern Europe, those aged <40 years, women, with CD4 cell count <350 cells/mm^3 or with cardiovascular disease or malignancy were significantly more likely to have been tested for SARS-CoV-2 infection. In this cohort it was also evident that access to testing had independent impact on detectability, as people with HIV in 2021 compared with those in 2020 were more likely to be tested (33).

In general, our findings showed that still not all PLWH receive ART. The situation is slightly worse in non-EU countries. This may explain the fact that PLWH with COVID-19 in non-EU countries were more often symptomatic and were more often hospitalized, especially that access to remdesivir was low in both EU and non-EU countries. This may mean that baseline care for PLWH is critical during events such as the pandemic.

In our study there are some limitations which should be mentioned. First of all, the conditions related to the epidemic period and the retrospective nature of the study may have resulted in underreporting of cases and to some extent to data completeness. Secondly, some people living with HIV with mild or asymptomatic course of COVID-19 disease could have been not registered in hospitals or out-patient clinics due to the fact, that they were not looking for medical care. Finally, both infectiveness and course of COVID-19 disease were highly related to the SARS-CoV-2 predominant variant influencing in turn both incidence, symptomatology and outcome. Our study was performed during the Delta wave. In the study Dobowolska et al. it was observed that in polish population consisted of 2225 patients, divided into two groups depending on the SARS CoV-2 variant, the Delta variant was associated with worse clinical course of COVID-19 and a higher risk of death than the Omicron variant. According to the study results patients infected with Omicron variant presented significantly less often in an unstable symptomatic state with SpO2 equal to or below 90% on admission (49.9% for Delta vs 29.9% for Omicron; P <0.001). What is also important the risk of death was significantly lower in the patients treated with antiviral drugs regardless of the pandemic wave (34).

Finally, access to anti-COVID-19 vaccination varied across specific population groups. As we know from studies performed in the region vaccination was available from December 2020 in 20 of 22 reviewed Central and Eastern European countries, but prioritized groups were medical staff. HIV patients become to be prioritized by few countries and later during pandemic (35).

However, in our study, we raised the important issue of differences among people living with HIV diagnosed with COVID-19 in European Union and non-European Union countries, which mainly contributes to differences in HIV care. A worrying fact is that general access to antiviral therapy in the region is low. Further research is desperately needed to ascertain benchmarking of care for the region as well as within the region both for European Union and non-European Union countries.

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Conceptualization: ASK, JK ; Data curation: , BL, GD, VM, CO, DG, RP, AV, IA, LP, IG, NR, NB, NB (Bolokadze), TH; Formal analysis: JK; Investigation: BL, GD, VM, CO, DG, RP, AV, IA, LP, IG, NR, NB, NB (Bolokadze), TH; Methodology: ASK, JK; Supervision: JK; Writing – original draft: ASK; Writing – review & editing: ASK, JK

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The Outcome of COVID-19 among People Living with HIV in European Union (EU) vs. non-European Union (non-EU) Countries

Purpose

The Central and Eastern Europe (CEE) region differs significantly in access to HIV and co-infections care and treatment. A worse access to HIV care during pandemic as well as poor access to modern cART and newest COVID-19 treatment strategies could have a negative impact on countries depending on their EU membership.

Methods

The study was approved by Bioethical Committee of Medical University of Warsaw and conducted between November 2020 and May 2021. ECEE Network Group was collecting observational data on HIV-positive patients diagnosed with COVID-19. In total, 16 countries from CEE submitted data on 557 HIV-positive patients using an electronic case report form (eCRF) built on the SurveyMonkey® platform. Chi-Square test was used for group comparisons.

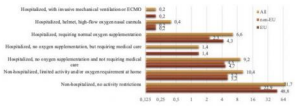
Table. Table. Factors associated with the course of COVID-19 disease among people living with HIV

Characteristic	Total N (%)	European Union Countries N (%)	Non-European Union Countries N (%)	p value
Total nr of patients	557 (100.0)	361 (100.0)	196 (100.0)	
Last HIV viral load				0.0135
• <50 copies/ml	472 (84.7)	317 (87.8)	155 (79.0)	
• >=50 copies/ml	85 (15.2)	45 (12.5)	40 (20.4)	
The last CD4 count				0.0170
• >=350 cells/ul	438 (78.6)	296 (82.0)	142 (72.5)	
• <=350 cells/ul	119 (21.4)	66 (18.3)	53 (27.0)	
Comorbidities				0.6939
• yes	158 (28.4)	105 (29.0)	53 (27.0)	
• no	399 (71.6)	257 (71.2)	142 (72.5)	
Symptomatic COVID-19				0.0009
• yes	484 (86.9)	302 (83.6)	182 (93.3)	
• no	73 (13.1)	60 (16.6)	13 (6.7)	
COVID-19 diagnosis				0.2621
• PCR SARS CoV-2	487 (87.6)	312 (86.4)	175 (89.3)	
• radiology	3 (0.5)	1 (0.3)	2 (1.0)	
• serology	54 (9.7)	40 (11.1)	14 (7.1)	
• symptoms	12 (2.2)	9 (2.5)	3 (1.5)	
HIV diagnosed during COVID-19				0.8029
• yes	18 (3.2)	11 (3.0)	7 (3.6)	
• no	539 (96.8)	351 (97.0)	188 (96.4)	
Hospitalisation				0.0027
• yes	138 (25.0)	75 (20.8)	63 (48.8)	
• no	413 (74.9)	284 (78.7)	129 (65.8)	
Remdesivir				0.1952
• yes	17 (3.0)	14 (3.9)	3 (1.5)	
• no	540 (96.9)	346 (96.1)	192 (98.5)	
Death/ICU				0.4877
• yes	21 (3.9)	12 (3.4)	9 (4.8)	
• no	517 (96.1)	337 (96.6)	180 (95.2)	

Results

In total 557 patients were included into the analyses: 361 from EU (Bulgaria, Croatia, Czech Republic, Estonia, Greece, Hungary, Lithuania, Poland, Romania, Serbia) and 196 from non-EU countries (Albania, Belarus, Bosnia and Herzegovina, Georgia, Turkey, Ukraine). In general, 426 (76.5%) patients were males, median age in years was 43,4 [IQR:6-86] and median BMI was 25,37 [13,5-60,1]. Median time since HIV diagnosis in years was 9,13 [0-33], median CD4 count before COVID-19 diagnosis was 635 [2-2099] copies/mm3 and 474 (85%) patients had undetectable viral load before COVID-19 diagnosis. In total 21 (3.9%) of patients died or have been treated in ICU, 17 (3.0%) received remdesivir. The comparison of EU and non-EU groups is presented in Table and baseline WHO Ordinal COVID-19 Scale is presented at Figure

Figure. Baseline WHO Ordinal COVID-19 Scale



Conclusions

Patients from non-EU countries were less likely to have suppressed HIV viral load and CD4 count above 350 cells/mm3, as compared to patients from EU countries. They were also more likely to be COVID-19 symptomatic and hospitalized. Access to remdesivir was comparable for both groups of countries, but very modest ranging from 1.5% to 3.9%.

Table 1. Baseline characteristics of people living with HIV included into the study in European Union Countries and Non-European Union Countries.

Characteristic	European Union Countries N=361	Non-European Union Countries N=196	Total N=557	p-value
Sex at birth N (%)				<0.00001
male	298 (82.5)	128 (65.3)	426 (76.5)	
female	63 (17.5)	68 (34.7)	131 (23.5)	
Age in years, median [IQR*]	42.6 [19-83]	44.81 [19-86]	43.4 [19-86]	0.6624
BMI** in kg/m^2, median [IQR]	25.3 [14.7-60.1]	25.49 [19-44.1]	25.37 [13.5-60.1]	0.4275
Time since HIV diagnosis in years median [IQR*]	9.73 [0-33]	8.01 [0.5-24]	9.13 [0-33]	0.3128
CD4 count before COVID-19 diagnosis median [IQR] copies/ml	659.78 [11-2093]	588.58 [11-1656]	635.03 [2-2093]	0.4268
CD4 count after COVID-19 diagnosis median [IQR] copies/ml	630.15 [2-2099]	534.75 [7-1414]	595.93 [2-2099]	0.4467

Table 2. Factors associated with HIV, COVID-19, comorbidities and socio-economic situation among people living with HIV in European Union Countries and Non-European Union Countries.

Characteristic	European Union Countries N (%)	Non-European Union Countries N (%)	Total N (%)	p value
Factors associated with HIV				
The last viral load				0.0135
<50 copies/ml	316 (87.8)	158 (79.0)	474 (85)	
>=50 copies/ml	45 (12.5)	40 (20.4)	85 (15.2)	
The last CD4 count				0.0170
>350 cells/ul	296 (82.0)	142 (75.2)	438 (78.6)	
=<350 cells/ul	66 (18.3)	53 (27.0)	119 (21.36	
Route of infection				<0.0001
heterosexual	80 (22.1)	97 (49.7)	117(31.8)	
IVDU***	46 (12.7)	39 (20.0)	85 (15.3)	
MSM****	219 (60.5)	48 (24.6)	267 (47.9)	
unknown	11 (3.0)	11 (5.6)	22 (3.95)	
other	6 (1.08)	0 (0.0)	6 (1.08)	
ARV	343 (94.7)	181 (92.8)	524 (94)	0.3537
HIV diagnosis during COVID-19	11 (3.0)	7 (3.6)	18 (3.23)	0.8029
Habits				

Using of psychoactive substances				0.0448
In the past	94 (25.9)	39 (20.0)	133 (23.9)	
never	228 (62.9)	141 (72.3)	369 (66.2)	
now	32 (8.8)	15 (7.7)	47 (8.4)	
unknown	8 (2.2)	0 (0)	8 (1.4)	
Smoking				0.0003
In the past	69 (19.0)	65 (33.3)	134 (24.06)	
never	164 (45.3)	71 (36.4)	235 (42.2)	
now	114 (31.5)	58 (29.7)	172 (30.9)	
unknown	15 (4.1)	1 (0.5)	16 (2.9)	
Comorbidities				
Comorbidity	105 (29.0)	53 (27.0)	158 (28.4)	0.6939
Viral coinfections (HBV and/or HCV)	44 (13.0)	31 (15.9)	75 (14.1)	0.0933
Socio-economic situation				
Current employed	273 (75.4)	136 (69.7)	409 (73.4)	0.1597
COVID-19 treatment				
Remdesivir	14 (3.9)	3 (1.5)	17 (3)	0.1952
% Patients with severe COVID-19 on Remdesivir	18.6	4.8	12.3	0.0275
Factors associated with COVID-19				
Death/ICU	12 (3.4)	9 (4.8)	21 (3.9)	0.4877

Hospitalization	75 (20.8)	63 (32.8)	138(25)	0.0027
COVID-19 diagnosis				0.2621
PCR SARS CoV-2	312 (86.4)	175 (89.3)	487 (87.59)	
radiology	1 (0.3)	2 (1.0)	3 (0.54)	
serology	40 (11.1)	14 (71.5)	54 (9.71)	
symptomps	9 (2.5)	3 (1.5)	12 (2.16)	
Symptomps at baseline	302 (83.6)	182 (93.3)	484 (86.89)	0.0009

Table 3. Comorbidities among people living with HIV diagnosed with COVID-19 in European Union Countries and Non-European Union Countries.

Comorbidities	UE countries (Total participants 361)	Non-UE countries (Total participants 196)	Total participants 557	p-value
Cardiovascular diseases	64 (17%)	32 (16%)	96 (17%)	0.7247
Respiratory diseases	23 (6.3%)	7 (3.5%)	30 (5.3%)	0.1835
Kidney diseases	11 (3%)	7 (3.5%)	18 (3.2%)	0.7464
Malignancies	13 (3.6%)	5 (2.5%)	18 (3.2%)	0.5163
Diabetes	19 (5.2%)	10 (5.1%)	29 (5.2%)	0.9381
Liver cirrhosis	5 (1.3%)	3 (1.5%)	8 (1.4%)	0.8919
HCV	30 (8.3%)	19 (9.6%)	49 (8.7%)	0.6148
HBV	12 (3.3%)	7 (3.5%)	19 (3.4%)	0.8820
HCV+HBV	7 (1.9%)	0 (0%)	7 (1.2)	0.1812
Other	19 (5.2%)	10 (5.1%)	29 (5.2%)	0.9341

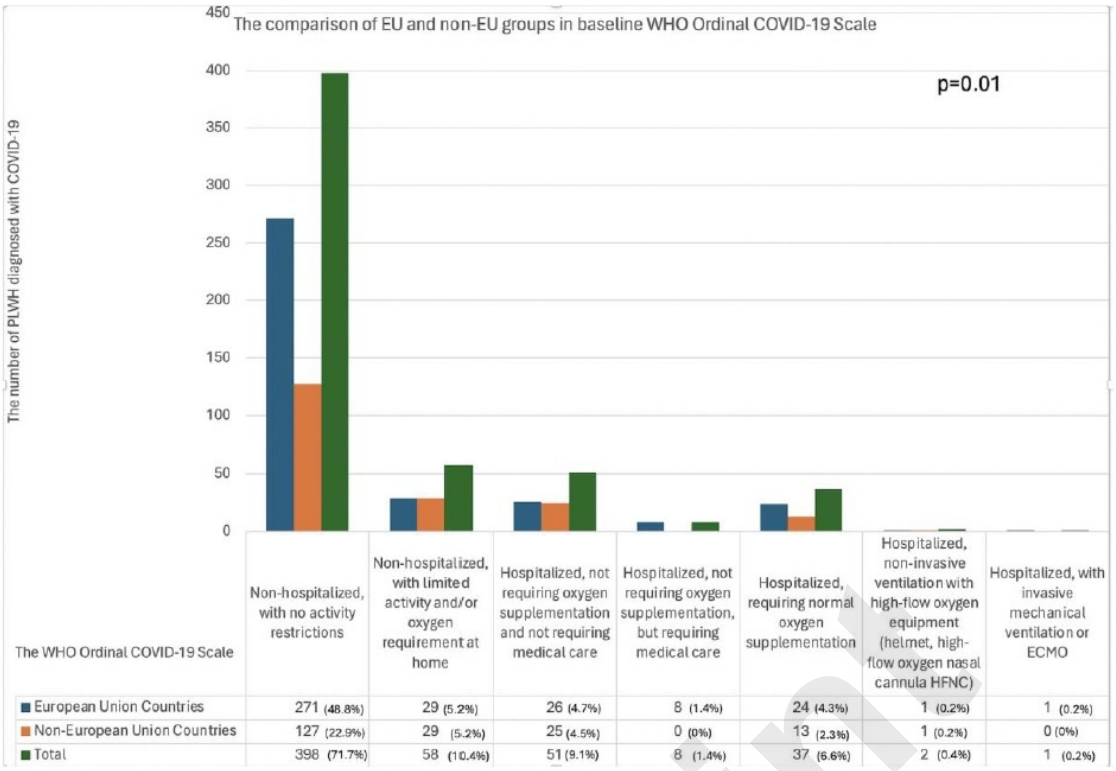


Figure 1. The comparison of WHO Ordinal COVID-19 Scale at baseline between European Union and non-European Union countries

The comparison of WHO Ordinal COVID-19 Scale at baseline between European Union and non-European Union countries