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The Use of Unproven Drugs for COVID-19 Treatment in People Living with HIV in Central and Eastern Europe

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Abstract

Early in 2020, the WHO recommended that existing drugs be evaluated as a repurposed resource to fight the SARS-CoV-2 pandemic. Here, we investigate the trends of using repurposed and off-label drugs among people living with HIV in Central and Eastern Europe (CEE). From November 2020 to May 2021, data on the clinical outcomes of HIV-positive patients diagnosed with COVID-19 were collected on eCRFs (SurveyMonkey® platform, Inc. San Mateo, CA, USA). Factors associated with the off-label drugs available at this

time (chloroquine, hydroxychloroquine, favipiravir, oseltamivir, and lopinavir/ritonavir) were identified using logistic regression models. Of the 557 HIV-positive patients assessed with COVID-19 disease, 67 (12.0%) received off-label drugs, as well as 11.6% (16/138) of hospitalized and 12.2% (51/419) of ambulatory patients ($p = 0.8564$). In the adjusted logistic regression model, higher odds of off-label drug use were found in patients who had their diagnoses confirmed by an RT PCR test (aOR 5.08 [95%CI 1.17–22.0], $p = 0.0396$), and who came from a non-EU region (aOR 6.79 [95%CI 3.51–13.1], $p < 0.0001$). The only factor decreasing the odds of off-label drug use was co-infection (aOR 0.31 [95%CI 0.10–0.94], $p < 0.0395$). In a cohort of HIV patients from the CEE, 12% were prescribed off-label drugs for COVID-19. Symptomatic patients with confirmed SARS-CoV-2 infection or who were from non-EU countries were more likely to receive a repurposed drug. Drug repurposing is an immediate solution to emerging pandemics. All data regarding the safety and effectiveness of such use should be monitored, reported, and publicly available. Access patterns within and outside the EU should be analyzed to prevent potential inequalities in access to care during epidemics in European settings.

Keywords: HIV; COVID-19; SARS-CoV-2; off-label; repurposed; repositioned

1. Introduction

On 11 March 2020, the global COVID-19 outbreak was declared a pandemic; soon, an overwhelming number of cases and deaths were seen in Europe [1]. The severity of the disease and the high mortality led to an urgent need to develop new drugs. Early in 2020, the World Health Organization recommended that existing drugs be evaluated as a repurposed resource to fight the SARS-CoV-2 pandemic. Drug repurposing, also known as repositioning, is the process of discovering new uses for existing drugs through immediate and short-term clinical trials. Compared to traditional de novo drug development approaches, this process saves time and cost [2]. Following the announcement of the Coordinated Global Research Roadmap 2019: Novel Coronavirus, repurposing of potential drug candidates became a common call with the initiation of the SOLIDARITY study—the world's largest trial for investigating drugs to be repositioned as COVID-19 therapies [3]. While waiting for the study's results, off-label drug use became common practice among medical practitioners, who were desperate to help their patients, and was widely supported by the governments' procurement and central distribution of various potential therapies [4,5]. Unfortunately, the SOLIDARITY trial showed that remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon regimens had no effect on 28-day mortality rates [6]. This further discouraged the medical community and caused frustration, resulting in clinical practice standards being continuously placed in jeopardy. Moreover, speculations based on pre-clinical reports were commonly used as evidence for prescribing drugs [7].

People living with HIV were perceived as having a higher risk of unfavorable COVID-19 outcomes due to the risk that viral shedding would persist for longer [8]. Although these findings were only confirmed for people with an uncontrolled HIV infection or low CD4 counts, these factors could affect treatment choices and influence off-label prescription patterns for this group of patients.

While repurposed drugs are of assistance in medical care, the use of off-label drugs poses substantial risks for both the patient and the care provider. The impact of this phenomenon remains unknown and is insufficiently researched, with outcomes rarely

being published. With this in mind, we decided to investigate the frequency and patterns of off-label drug use among people living with HIV in Central and Eastern Europe.

2. Materials and Methods

The Euroguidelines in Central and Eastern Europe (ECEE) Network Group, established in 2016, consists of healthcare providers from 24 countries who are actively involved in the field of HIV care. From November 2020 to May 2021, data on the clinical outcomes of people living with HIV diagnosed with COVID-19 were collected on electronic case report forms (eCRF) (SurveyMonkey® platform). All patients known by an HIV center as being diagnosed with COVID-19, irrespective of the place of their diagnosis, were included in the study (both retrospectively and prospectively). We collected data from 22 HIV clinics in 16 countries (Albania, Belarus, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Greece, Hungary, Lithuania, Poland, Romania, Serbia, Turkey, and Ukraine). A detailed methodology of the study has been published elsewhere [9,10]. Off-label drugs included chloroquine, hydroxychloroquine, favipiravir, oseltamivir, and lopinavir/ritonavir [5].

The data collected included baseline characteristics and factors associated with the odds of prescribing off-label drugs for COVID-19 treatment in a cohort of HIV-positive patients from the CEE. The factors investigated were gender, age, body mass index (BMI), presence of comorbidities, presence of co-infections, region of care, employment status, history of using psychoactive substances, HIV transmission risk group, CD4+ cell count, virial suppression, antiretroviral treatment, real-time reverse transcriptase polymerase chain reaction (RT PCR) SARS-CoV-2 result, and presence of symptomatic COVID-19. In the statistical analyses, the groups were compared using non-parametric tests: Chi-square and Kruskal–Wallis tests, as appropriate. Logistic regression models were used to identify the factors associated with prescribing off-label drugs. The multivariate model was adjusted by all the factors identified as significant in univariate models ($p < 0.1$). All statistical tests were two-sided, and a p value of <0.05 was accepted as significant for group comparison and the final logistic regression model. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

The study was approved by the Bioethical Committee of The Medical University of Warsaw (Nr AKBE/155/2020). Informed consent was waived based on the retrospective and non-interventional characteristics of this study.

3. Results

In a cohort of 557 HIV positive patients from Central and Eastern Europe diagnosed with COVID-19 disease, reported between November 2020 and May 2021, 67 (12.0%) were prescribed off-label drugs; this included 11.6% (16/138) of hospitalized and 12.2% (51/419) of ambulatory patients ($p = 0.8564$).

Of the total number of patients, 428 (76.8%) were male, 267 (47.9%) acquired HIV through men who have sex with men (MSM) contacts, 180 (32.3%) had ever used or were using psychoactive substances, 524 (94.1%) were on combination antiretroviral therapy (cART), 473 (84.7%) had an HIV viral load (VL) of <50 copies/mL, and 388 (69.6%) had a CD4 count of >350 cells/mm^3.

Those who received off-label drugs were prescribed favipiravir (n = 37), chloroquine/hydroxychloroquine (n = 15), lopinavir/ritonavir (n = 11), or oseltamivir (n = 8). In this subgroup, 54 (80.1%) were male, 43.3% were infected through heterosexual contact, 34.3% were infected through MSM contact, 14.9% were infected by injecting drugs, and the cause of infection for 7.5% was other/unknown. The median age was 40.0 (35.0–56.0) years.

Most of the patients in the cohort were from non-European Union (EU) countries (77.6%) (Table 1).

Table 1. Baseline characteristics stratified by off-label drug use.

	All N = 557	Not Receiving Off-Label Drug N = 490	Receiving Off-Label Drug N = 67	*p* Value
Female sex, n (%)	129 (23.1)	116 (23.7)	13 (19.7)	0.5366
Age in years, median (IQR)	42.0 (35.0–50.0)	42.0 (36.0–49.0)	40.0 (35.0–56.0)	0.6624
BMI, median (IQR)	24.8 (22.0–28.0)	24.7 (22.0–27.9)	25.0 (23.0–28.5)	0.4275
Non-EU country, n (%)	195 (35.0)	143 (29.2)	52 (77.6)	<0.0001
Currently employed, n (%)	409 (73.4)	364 (74.3)	45 (67.2)	0.2383
Any comorbidity, n (%)	158 (28.4)	137 (28.0)	21 (31.3)	0.5654
Time since HIV diagnosis	8.0 (4.0–13.0)	8.0 (4.0–13.0)	6.5 (3.0–13.0)	0.3128
Mode of HIV transmission, n (%)				0.1306
Heterosexual	177 (31.8)	148 (30.2)	29 (43.3)	
IDU	85 (15.3)	75 (15.3)	10 (14.9)	
MSM	267 (47.9)	244 (49.8)	23 (34.3)	
Other/Unknown	28 (5.0)	23 (4.7)	5 (7.5)	
HIV diagnosis during COVID-19, n (%)	18 (3.2)	16 (3.3)	2 (3.0)	0.9032
On antiretroviral therapy, n (%)	524 (94.1)	458 (88.0)	66 (98.5)	0.1616
HIV VL < 50 copies/mL, n (%)	472 (84.7)	416 (84.9)	56 (83.6)	0.7206
CD4 > 350 cells/mm^3, n (%)	438 (78.6)	388 (79.2)	50 (74.6)	0.4268
Psychoactive substance use, n (%)				0.0928
In the past	133 (78.6)	123 (25.1)	10 (14.9)	
Never	369 (66.2)	318 (64.9)	51 (76.1)	
Currently	8 (1.4)	8 (1.6)	0 (0.0)	
Unknown				
Positive SARS-CoV-2 RT PCR, n (%)	487 (87.4)	422 (86.3)	65 (97.0)	0.0317
Presence of COVID-19 symptoms, n (%)	484 (86.9)	420 (85.7)	64 (95.5)	0.0210
Hospitalization, n (%)	138 (24.8)	122 (25.2)	16 (23.9)	0.8813
Need for oxygen therapy at baseline, n (%)	40 (7.2)	38 (7.8)	2 (3.0)	0.6942
Steroid therapy for COVID-19, n (%)	89 (16.0)	73 (14.9)	16 (23.9)	0.0741
Remdesivir therapy, n (%)	17 (3.0)	16 (3.3)	1 (1.5)	0.7078
Death/ICU, n (%)	21 (3.8)	21 (4.4)	0 (0.0)	0.0936

Off-label drugs include chloroquine, hydroxychloroquine, favipiravir, oseltamivir, and lopinavir/ritonavir.

The group of patients who were prescribed off-label drugs and the group who were not did not differ in terms of gender, age, BMI, presence of comorbidities, employment status, or history of using psychoactive substances. HIV-related factors such as mode of HIV transmission, baseline CD4 cell count, and HIV viral load, as well as antiretroviral treatment components, also showed no statistical differences (Table 1). There were also no associations between the two groups regarding the patterns of prescribing remdesivir or steroids.

In the univariate regression models, the presence of co-infections (OR 0.30 [95%CI 0.11–0.85], $p < 0.0234$), being from a non-EU region (OR 8.41 [95%CI 4.59–15.4], $p < 0.0001$), a diagnosis confirmed by an RT PCR test (OR 10.77 [95%CI 2.60–44.6], $p = 0.0011$), symptomatic COVID-19

(OR 3.56 [95%CI 1.09–11.6], $p = 0.0359$), and a heterosexual vs. MSM mode of HIV transmission (OR 2.08 [95%CI 1.16–3.73], $p = 0.0141$) were significantly associated with the prescribing of off-label drugs. After adjustment, the only significant factors identified by the multivariate model that increased the odds of off-label drug use were a diagnosis confirmed by an RT PCR test (aOR 5.08 [95%CI 1.17–22.0], $p = 0.0396$) and being from a country in a non-EU region (aOR 6.79 [95%CI 3.51–13.1], $p < 0.0001$). The only factor that decreased the odds of off-label drug use was the presence of co-infection (aOR 0.31 [95%CI 0.10–0.94], $p < 0.0395$) (Table 2).

Table 2. Factors associated with the odds of prescribing off-label drugs for COVID-19 treatment in a cohort of HIV-positive patients from the CEE.

Baseline Factors	OR (95% CI)	*p* Value	aOR (95%CI)	*p* Value
General factors				
Male sex	1.27 (0.67–2.41)	0.4684	-	-
Age in years	1.00 (0.98–1.02)	0.8745	-	-
BMI by 1 unit	1.01 (0.96–1.07)	0.5966	-	-
Comorbidity (any) *	1.18 (0.68–2.04)	0.5647	-	-
Co-infection (any) **	0.30 (0.11–0.85)	0.0234	0.31 (0.10–0.94)	0.0395
Non-EU region residency	8.41 (4.59–15.4)	<0.0001	6.79 (3.51–13.1)	<0.0001
Employed vs. Unemployed/Unknown	0.71 (0.41–1.22)	0.2172	-	-
Psychoactive substances Ever vs. Never/Unknown	0.62 (0.34–1.13)	0.1181	-	-
HIV-related factors				
Mode of HIV acquisition				
Heterosexual vs. MSM	2.08 (1.16–3.73)	0.0141	0.85 (0.42–1.69)	0.6420
IDU vs. MSM	2.36 (0.74–7.56)	0.1490	1.42 (0.38–5.28)	0.5968
Other/Unknown vs. MSM	1.46 (0.68–3.12)	0.3312	0.88 (0.37–2.10)	0.7751
CD4+ $\leq$ 350 cells/mm^3	1.29 (0.72–2.34)	0.3942	-	-
CD4+ lymphocyte count by 100 units increase	1.00 (0.92–1.08)	0.9663	-	-
HIV VL > 50 copies/mL	1.10 (0.55–2.21)	0.7788	-	-
On antiretroviral therapy	4.61 (0.62–34.3)	0.1355	-	-
COVID-19-related factors				
Positive RT PCR SARS-CoV-2	10.8 (2.60–44.6)	0.0011	5.08 (1.17–22.0)	0.0296
Symptomatic COVID-19	3.56 (1.09–11.6)	0.0359	1.82 (0.51–6.47)	0.3539

* Comorbidities included non-communicable, chronic disease. ** Co-infections included HCV and/or HBV.

4. Discussion

In our cohort, one in ten patients living with HIV in Central and Eastern Europe was prescribed an off-label drug for COVID-19 disease. The majority of patients were on effective antiretroviral treatment with high CD4+ lymphocyte counts. This strategy encompasses major risk because, apart from off-label drugs potentially having no proven effect on SARS-CoV-2, they have potential toxicities and drug–drug interactions, especially among patients on antiretroviral therapy [9,11].

Interestingly, there was no relation between traditional HIV-related factors and off-label drug use. However, our analysis showed that patients with a confirmed SARS-CoV-2 infection who were from a non-EU country were more likely to receive off-label drugs. This may suggest that off-label drugs were used due to their expected antiviral effect and, therefore, prescribers or local guidelines favored patients with virological confirmation. If so, it remains unclear why patients with comorbidities, clearly with a higher expected

benefit, were not prioritized to receive off-label treatment. On the contrary, having a co-infection decreased the odds of receiving off-label treatment by almost 70%. This may reflect a fear of drug–drug interactions and unknown toxicities (e.g., hepatotoxicity), and, in turn, suggests that access to certain forms of treatment is limited for patients from different subgroups. Another option is that some substances were only made available through inpatient care, which is country-specific.

As the off-label implementation claimed to target SARS-CoV-2 replication, we would expect it to be used very early in the course of the infection, preferably within the first 3–5 days of symptoms. In our study, hospitalized patients, who were usually admitted in the second week of the disease, were as likely to receive treatment as ambulatory patients. Although several factors could explain this, such as a drug's access and distribution channels, this may also indicate that there was no systematic plan for such interventions. Facing contradictory information coming from the scientific world, as well as mass media pressure, many European governments decided to procure large batches of drugs centrally and give permission to use them off-label in SARS-CoV-2-positive individuals, but surveillance of their effectiveness and toxicities was not planned in a prospective or proactive way [12,13]. Access, indications, and substance choice varied depending on the local availability of the substance and earlier experience of its use, such as the case with favipiravir [14].

While the approval of new drugs is a slow and time-consuming process, there are mechanisms in place for repurposing drugs, developed originally for other infections, as new therapeutic indications [2,15–17]. One of these mechanisms is compassionate use, which, in cases of severe epidemics, is considered acceptable by international and national authorities [4]. However, compassionate use needs to fulfill two important conditions: the new medicinal product being investigated must be part of ongoing clinical trials, and it can only be used in serious or life-threatening conditions [18]. As indicated in our study, the majority of patients who were prescribed off-label medication were symptomatic but did not require hospitalization, and 60% did not have any underlying conditions. Therefore, the conditions for "compassionate use" were not met. Another strategy for drug repurposing is the expanded access pathway. However, this pathway is to allow terminally ill patients who do not qualify for clinical trials to access interventions.

During the COVID-19 pandemic, several substances were considered to have potential activity against the SARS-CoV-2 infection. Chloroquine and hydroxychloroquine, well-known as anti-malarial agents, present activity against several RNA viruses. According to in vitro studies, they can interfere with the early phase of SARS-CoV-2 replication [19]. Favipiravir is approved in Japan for the treatment of influenza. This drug functions as a chain terminator at the site where viral RNA is incorporated and reduces the viral load [20]. Oseltamivir is an ethyl ester oral prodrug that acts against the neuraminidase in influenza A and B viruses and is widely approved for the treatment and prophylaxis of these influenza viruses. Oseltamivir was administered for COVID-19 with or without antibiotics and corticosteroids, and was used in a clinical trial in combination with chloroquine and favipiravir [21]. Lopinavir/ritonavir is an HIV protease inhibitor, used in the treatment of HIV-1 infections; despite some structural differences between HIV and SARS-CoV-2 proteases, this drug was considered to be potentially active against the latter [22]. All the above-mentioned drugs were utilized during the early phase of the COVID-19 pandemic, with no in vivo confirmation of their clinical effect through unstructured access mechanisms [4].

It must be mentioned that all the drugs discussed above have already been approved for evidence-based indications. Therefore, rational prescribing of these drugs must be practiced, and it needs to be ensured that patients receiving these drugs for their labeled use have priority access [5].

An important observation in our study was that access to remdesivir, the first repurposed drug available in the region, was very limited. Only 3% of patients in our cohort (one patient in the off-label group) received it. One could expect that limited access to remdesivir might also have contributed to the frequent use of unproven treatment options.

Due to the observational and retrospective design of this study, we were not able to collect reliable data on adverse events related to off-label drug use, nor compare their effectiveness with standards of care. This is an important limitation, but also indicates the necessity of ongoing development of tools, such as *Monitored Emergency use of Unregistered and Investigational Interventions* (MEURIs) developed by the WHO in response to the emergence of the Ebola virus.

Further limitations include the small study sample, which may limit the generalizability of our conclusions. However, the aim of our work was to investigate the access and prescription patterns of off-label drugs among people living with HIV in regions limited to Central and Eastern Europe. The data on off-label COVID-19 treatments for this group of patients and in the European region are limited. At the same time, people living with HIV are rarely recruited for clinical trials of therapies for emerging pathogens, such as SARS-CoV-2. For example, only 32 HIV positive patients were included in the RECOVERY trial, and subgroup analysis was not available for this group of patients [23]. Finally, in regard to study limitations, we need to underline that during the study period, between 2020 and 2021, the national guidelines were shifting substantially. Following these differences across 16 countries from the region (both EU and non-EU) is beyond our ability.

5. Conclusions

While drug repositioning seems to be a tempting and immediate solution for emerging new pathogens and diseases, there is a common misunderstanding about the difference between this process and simple off-label use. As indicated by the WHO document for public health emergencies, MEURI, it is the moral duty of both medical practitioners and public health systems to report outcome data from off-label drug use [24,25]. Finally, investigating patterns for off-label drug use may help to identify gaps in care and inequalities in treatment access for different countries within Europe.

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Data Availability Statement: Data supporting the reported results can be found onsite at Medical University of Warsaw.

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