

HIV treatment strategies across Central, Eastern and Southeastern Europe: New times, old problems

Papadopoulos, Antonios; Thomas, Konstantinos; Protopapas, Konstantinos; Antonyak, Sergii; Begovac, Josip; Dragovic, Gordana; Gökengin, Deniz; Aimla, Kersti; Krasniqi, Valbon; Lakatos, Botond; ...

Source / Izvornik: **HIV Medicine, 2022, 24, 462 - 470**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1111/hiv.13416>

Permanent link / Trajna poveznica: <https://urn.nsk.hr/urn:nbn:hr:105:765207>

Rights / Prava: [Attribution-NonCommercial 4.0 International/Imenovanje-Nekomercijalno 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2025-03-12**



Repository / Repozitorij:

[Dr Med - University of Zagreb School of Medicine Digital Repository](#)



ORIGINAL ARTICLE

HIV treatment strategies across Central, Eastern and Southeastern Europe: New times, old problems

Antonios Papadopoulos¹ | Konstantinos Thomas¹ | Konstantinos Protopapas¹ |
 Sergii Antonyak² | Josip Begovac³ | Gordana Dragovic⁴ | Deniz Gökengin⁵ |
 Kersti Aimla⁶ | Valbon Krasniqi⁷ | Botond Lakatos⁸ | Mariana Mardarescu⁹ |
 Raimonda Matulionyte¹⁰ | Velida Mulabdic¹¹ | Cristiana Oprea¹²  |
 Aleksandr Panteleev¹³ | Dalibor Sedláček¹⁴ | Lubomir Sojak¹⁵ |
 Agata Skrzat-Klapaczyńska¹⁶  | Anna Vassilenko¹⁷ | Nina Yancheva¹⁸ |
 Oleg Yurin¹⁹ | Andrzej Horban¹⁶ | Justyna D. Kowalska¹⁶  | for the
 Euroguidelines in Central and Eastern Europe Network Group

¹4th Department of Internal Medicine, University General Hospital Attikon, Medical School, National and Kapodistrian University of Athens, Athens, Greece

²Gromashevsky Institute of Epidemiology and Infectious Diseases, Viral Hepatitis and AIDS Department, Kiev, Ukraine

³University Hospital for Infectious Diseases, Zagreb, Croatia

⁴Department of Pharmacology, Clinical Pharmacology and Toxicology, School of Medicine, University of Belgrade, Belgrade, Serbia

⁵Ege University, Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Izmir, Turkey

⁶West Tallinn Central Hospital, Tallinn, Estonia

⁷Infectious Diseases Clinic, University Clinical Center at Kosovo, Prishtina, Kosovo

⁸National Institute of Hematology and Infectious Diseases, South-Pest Central Hospital, National Center of HIV, Budapest, Hungary

⁹National Institute for Infectious Diseases Matei Bals, Bucharest, Romania

¹⁰Vilnius University, Faculty of Medicine, Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania

¹¹Clinic for Infectious Diseases, Clinical Center, University of Sarajevo, Sarajevo, Bosnia and Herzegovina

¹²Carol Davila University of Medicine and Pharmacy, Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest, Romania

¹³City TB Hospital # 2, St-Petersburg, Russia

¹⁴Department of Infectious Diseases and Travel Medicine, Charles University of Prague, Prague, Czech Republic

¹⁵Department of Infectology and Geographical Medicine, Academic L. Derer's University Hospital, Bratislava, Slovakia

¹⁶Department of Adults' Infectious Diseases, Hospital for Infectious Diseases, Medical University of Warsaw, Warsaw, Poland

¹⁷Republican Scientific and Practical Center for Medical Technologies, Global Fund Grant Management Department, Belarusian State Medical University, Minsk, Belarus

¹⁸Department for AIDS, Specialized Hospital for Active Treatment of Infectious and Parasitic Diseases, Sofia, Bulgaria

¹⁹Central Research Institute of Epidemiology, Moscow, Russia

Correspondence

Antonios Papadopoulos, Associate Professor in Internal Medicine and Infectious Diseases, National and Kapodistrian University of Athens,

Abstract

Introduction: In the last decade, substantial differences in the epidemiology of, antiretroviral therapy (ART) for, cascade of care in and support to people

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2022 The Authors. *HIV Medicine* published by John Wiley & Sons Ltd on behalf of British HIV Association.

4th Department of Internal Medicine,
University General Hospital Attikon,
1 Rimini Str., 124 62 Chaidari, Athens,
Greece.
Email: antpapal@otenet.gr

with HIV in vulnerable populations have been observed between countries in Western Europe, Central Europe (CE) and Eastern Europe (EE). The aim of this study was to use a survey to explore whether ART availability and therapies have evolved in CE and EE according to European guidelines.

Methods: The Euroguidelines in Central and Eastern Europe (ECEE) Network Group conducted two identical multicentre cross-sectional online surveys in 2019 and 2021 concerning the availability and use of antiretroviral drugs (boosted protease inhibitors [bPis], integrase inhibitors [INSTIs] and nucleoside reverse transcriptase inhibitors [NRTIs]), the introduction of a rapid ART start strategy and the use of two-drug regimens (2DRs) for starting or switching ART. We also investigated barriers to the implementation of these strategies in each region.

Results: In total, 18 centres participated in the study: four from CE, six from EE and eight from Southeastern Europe (SEE). Between those 2 years, older PIs were less frequently used and darunavir-based regimens were the main PIs (83%); bictegravir-based and tenofovir alafenamide-based regimens were introduced in CE and SEE but not in EE. The COVID-19 pandemic did not significantly interrupt delivery of ART in most centres. Two-thirds of centres adopted a rapid ART start strategy, mainly in pregnant women and to improve linkage of care in vulnerable populations. The main obstacle to rapid ART start was that national guidelines in several countries from all three regions did not support such a strategy or required laboratory tests first; an INSTI/NRTI combination was the most commonly prescribed regimen (75%) and was exclusively prescribed in SEE. 2DRs are increasingly used for starting or switching ART (58%), and an INSTI/NRTI was the preferred regimen (75%) in all regions and exclusively prescribed in SEE, whereas the use of bPis declined. Metabolic disorders and adverse drug reactions were the main reasons for starting a 2DR; in the second survey, HIV RNA <500 000 c/ml and high cluster of differentiation (CD)-4 count emerged as additional important reasons.

Conclusions: In just 2 years and in spite of the emergence of the COVID-19 pandemic, significant achievements concerning ART availability and strategies have occurred in CE, EE and SEE that facilitate the harmonization of those strategies with the European AIDS Clinical Society guidelines. Few exceptions exist, especially in EE. Continuous effort is needed to overcome various obstacles (administrative, financial, national guideline restrictions) in some countries.

KEYWORDS

AIDS, antiretroviral drugs, antiretroviral therapy, Central Europe, COVID-19, Eastern Europe, HIV infection, initial therapy, maintenance therapy, rapid ART strategy, southeastern Europe, switch therapy

INTRODUCTION

In the 40 years since the first cases of acquired immune deficiency syndrome (AIDS) were reported, remarkable progress has been made in the global response to the human immunodeficiency virus (HIV) epidemic. This

progress has been achieved through the implementation of HIV prevention programmes, efficient treatment of opportunistic infections and viral hepatitis, scale-up administration of combination antiretroviral therapy (ART) for HIV treatment and prevention and extensive HIV testing and counselling [1]. In 2014, the Joint

National Program on HIV/AIDS (UNAIDS) established the global 90–90–90 targets, that is, 90% of all people living with HIV to be diagnosed, 90% of them to receive ART and 90% of the latter to achieve viral suppression by 2020 [2]; these targets were recently updated to 95–95–95 [3]. These targets have been reached in some developed countries, but significant inequalities exist in many parts of the world [1].

The HIV situation in Europe is diverse [4]. In the European AIDS Clinical Society (EACS) Standard of Care Meeting in Brussels in 2016, it was highlighted that ART access in Eastern Europe (EE) was unacceptably low (20%–47%) across countries and that rates of viral suppression were very low rates because of the limited availability of treatment, criminalization and exclusion of vulnerable population at risk as stated below [5]. ART coverage was better (60%–69%) in Central Europe (CE). In 2018, an online survey disseminated by the European Centre for Disease Prevention and Control in 52 European and Central Asian countries revealed that, overall, 80% of people living with HIV were diagnosed, of whom 64% received ART and 86% of those treated were virally suppressed, but subregional outcomes varied [6]. The 90–90–90 corresponding results were 87–91–93 in the West, 83–75–75 in CE and 76%–46%–78% in EE. Likewise, the Euroguidelines in Central and Eastern Europe (ECEE) Conference in Warsaw in 2016, held under the auspices of EACS, highlighted that the HIV situation significantly differed in CE and EE from that in Western Europe in many respects, including epidemiology, mode of transmission, testing, ART (availability of drugs, treatment initiation, various regimens), cascade of care and organization and treatment access for vulnerable populations (e.g. people with HIV and viral hepatitis, people who inject drugs [PWID], migrants and prisoners) [7]. Another online survey report of the ECEE Network Group noted that the percentage of people virologically suppressed while on ART was 70%–95% in CE, 32%–95% in EE and 62%–97% in Southeastern Europe (SEE) [8].

These differences in the care of people living with HIV can be accounted for by several factors, including that the newest antiretrovirals or new fixed-dose combinations (FDCs) are not available or are available with some restrictions in some areas of CEE, there are limitations in first-line ART choice in other countries and that people living with HIV exhibit poor adherence to therapy and are frequently lost to follow-up because of stigma and social discrimination [5, 7, 9].

The EACS guidelines have also contained novel strategies, in concordance with other national and international guidelines, including rapid ART start and two-drug regimens (2DRs) for starting or switching ART [10–12]. The differences in the care of people living with HIV in CE make EACS guidelines difficult to implement [7].

The aim of our study was to use online surveys in 2019 and 2021 to ascertain whether recent advances in the management of HIV infections in CE, EE and SEE had an impact on ART availability and the introduction of novel therapeutic strategies according to EACS guidelines in daily practice.

METHODS

The ECEE Network Group (<https://www.eceenetwork.com>) was established in 2016 and involves experts in HIV infection and infectious diseases from 24 countries in this region. Its scope is to supervise and harmonize the standards of HIV care and viral hepatitis in the region. The ECEE activities include collaborative research projects, support of local activism and reinforcement of governmental actions, and it is endorsed by EACS and other European entities. The group collects data in the area of HIV and infectious diseases care through online surveys developed on the SurveyMonkey® platform. This project was started in 2019 as a result of in-person meetings and mutual agreement on the next year's priorities for the group. The year 2021 was chosen because the group felt that the COVID-19 pandemic could have an impact on access to certain ART strategies and procurement patterns. During an in-person meeting in 2019 in Warsaw, the group decided to conduct a multicentre cross-sectional survey on access to ART components and treatment strategies across the region. In 2021, the group decided to conduct the survey again to investigate the possible effects of the COVID-19 pandemic on access to certain ART strategies and medicines procurement.

For the current work, physicians from participating centres were asked to complete a questionnaire from two different timepoints, March 2019 and September 2021. The same practitioner answered the survey at each timepoint.

The participating countries were subdivided into CE (four centres, from the Czech Republic, Hungary, Poland and Slovakia), EE (six centres, from Belarus, Estonia, Lithuania, Russia and Ukraine) and SEE countries (eight centres, from Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Romania, Serbia and Turkey). Only centres that provided answers to both timepoints are included in this report.

The questionnaire included the following questions (the prespecified answers to these questions are cited in the supplement):

- Which protease inhibitors (PIs) are currently available and prescribed in your country?
- Which integrase inhibitors (INSTIs) are currently available and prescribed in your country?

- Which nucleos(t)ide reverse transcriptase inhibitors (NRTIs) are currently available and prescribed in your country?
- In your practice, did you experience any delay in anti-retroviral drug delivery that resulted in treatment interruptions or forced switching combination ART?
- Do you use rapid ART start? (defined as starting ART at the first visit in an HIV clinic with confirmed HIV infection with no other test results or pending other test results) and, if yes, in which circumstances or which risk groups?
- What is your preferred choice of ART for rapid start?
- Please describe possible obstacles to using rapid start.
- Do you use 2DRs (defined as two active antiretrovirals in a regimen) for starting or switching ART as regular daily clinical practice and, if yes, which 2DR do you use?
- What were the reasons for starting or switching to 2DRs?

In each category, participants could choose more than one answer. The results are presented per total number of participating centres and by region (CE, EE, SEE). Given the restricted number of participating centres, the observational nature of the report and the absence of pre-defined endpoints, we did not conduct any statistical analysis, and we present the results solely in a descriptive manner.

RESULTS

Participating centres

A total of 18 centres participated in the study: four from CE, six from EE and eight from SEE. All countries were represented by one centre, except for Russia and Romania, which were represented by two centres each. In the 2019 survey, three centres (17%) reported <20 visits from people living with HIV, seven (39%) reported 20–50 visits, four (22%) reported 50–100 visits and four (22%) reported >100 visits per week. In 2021, the respective distribution of centres was 11%, 29%, 50% and 11%; the number of centres with <20 visits, 20–50 visits and >100 visits per week decreased; and the number of centres with 50–100 visits per week increased.

Trends in ART prescription (Supplement Table)

Regarding PI, prescriptions of darunavir (DRV) and DRV/cobicistat (DRV/c) increased between 2019 and 2021, with the number of centres increasing from

12 (67%) to 15 (83%) and from 8 (44%) to 10 (56%), respectively. Moreover, the use of older PIs (lopinavir/ritonavir [LPV/r] and saquinavir [SQV]) decreased from 16 (89%) to 12 (67%) and from five (28%) to one (6%), respectively. The proportion of centres that prescribed atazanavir (ATV) or ATV/cobicistat did not essentially change.

The use of most INSTI antiretrovirals was relatively steady, with the exception of a slight decrease in prescriptions of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil (ELV/c/FTC/TDF) from seven (39%) to five (28%), without an increase in the similar single-tablet regimen containing tenofovir alafenamide (TAF) (ELV/c/FTC/TAF; 50% at both timepoints). The latter is largely underrepresented in EE in both periods. In total, 17 (94%) and 15 (83%) centres were using dolutegravir (DTG) and raltegravir (RAL) twice daily in 2019, whereas the respective rates were 100% and 94% in 2021. The bictegravir (BIC)-based single-tablet regimen was not available in all regions in 2019 but was already in supply in 10 of 18 (55%) participating centres in 2021, mainly in CE and SEE and in only one centre in EE.

The most significant finding regarding NRTI use was the introduction of TAF/FTC during this time interval, with 8 of 18 (44%) participating centres, but none in EE, using it in 2021. We also noticed a reduction in the use of the zidovudine/lamivudine (ZDV/3TC) combination, from 89% to 61%.

Interestingly, only a few centres reported delays in ART delivery resulting in treatment interruptions or forced switching ART (5/18 [28%] in 2019; 3/18 [17%] in 2021). No centre from CE reported delays in 2021.

We then attempted to describe the patterns of ART strategies between the three regions included in the study. The use of older PIs (LPV/r, SQV) decreased in CE and SEE, whereas the use of LPV/r remained stable in EE.

We found no significant differences in INSTI-based ART between the two time points in any of the three regions but did notice notable variations in the type of INSTI used. More specifically, ELV-based regimens were prescribed in all four CE centres. In contrast, only one in six centres in EE reported this type of INSTI-based ART, and the number of centres in SEE prescribing ELV declined from five to four of eight. A significant discordance was also noted regarding the availability of BIC in 2021 (CE: 4/4, EE: 1/6, SEE: 5/8). A similar discordance was also found in the use of TAF/FTC, where none of the six EE centres reported its prescription in any of the evaluations.

Trends in rapid ART start implementation

The number of centres reporting the implementation of rapid ART start increased from 9 (50%) to 12 (67%)

between the two time points. INSTI-based rapid ART start was the most common in both 2019 (7/9 [77%]) and 2021 (9/12 [75%]), with the remaining being PI-based regimens. Only one centre reported non-nucleoside reverse transcriptase inhibitor (NNRTI)-based ART rapid start in 2019. All CE countries used a PI-based regimen for rapid ART start; conversely, all SEE countries used an INSTI-based regimen and EE countries used both regimens in both time points. A tenofovir-based combination (TDF/FTC, TAF/FTC and TDF/3TC) was almost exclusively used as the NRTI backbone.

In 2019 the most common circumstances for the use of rapid ART start were pregnancy (7/9 [78%]), improved linkage and retention to care of PWID (3/9 [33%]) and men who have sex with men (MSM) with high-risk sexual behaviours (4/9 [44%]) and social factors (2/9 [22%]). The respective responses during the 2021 evaluation were 9/12 (75%), 3/12 (25%), 6/12 (50%) and 7/12 (58%).

Participants were also asked to report the potential obstacles to using rapid ART start. Among the most common reasons in the first evaluation were that the current national treatment programme required a test result before starting ART ($n = 8$ [44%]), that there was no need for rapid start (e.g. high-income country, low-incidence epidemic; $n = 3$ [17%]) and the absence of adequate ART components to perform rapid start ($n = 3$ [17%]). In the second evaluation, the most commonly reported reasons were that the current national treatment programme required a test result before starting ART ($n = 7$ [39%])

and that the national guidelines did not support rapid start ($n = 5$ [28%]).

2DR regimens for ART initiation and switching

The number of centres that used 2DR for ART initiation increased from 5 (28%) in 2019 to 10 (55%) in 2021 (Figure 1). In the first time point, an INSTI/NRTI combination was the most commonly prescribed ($n = 4$ [80%]), followed by boosted PI/INSTI ($n = 3$ [60%]) and boosted PI/NRTI ($n = 2$ [40%]). At the follow-up evaluation, we observed an increase in the use of INSTI/NRTI combination ($n = 9$ [90%]), whereas the respective values for both boosted PI/INSTI and boosted PI/NRTI were 1 of 10 (10%). No centre in 2019 and only one in 2021 reported the use of a boosted PI/NNRTI combination for ART start.

Regarding the reasons for considering ART initiation with 2DR in 2019 and 2021, concerns about metabolic profile (28% vs 28%) and adverse events (16% vs 22%, respectively) were the most frequently reported, and none of the participating centres referred to resistance as a concern. Interestingly, a compatible patient profile with viral load <500 000 c/ml and high cluster of differentiation (CD)-4 count as a reason for 2DR start was considerably increased between the two time points (6% vs 44%, Table 1). Other reasons included the presence of chronic kidney disease, avoidance of drug–drug interactions and the simplicity and tolerability of the regimen.

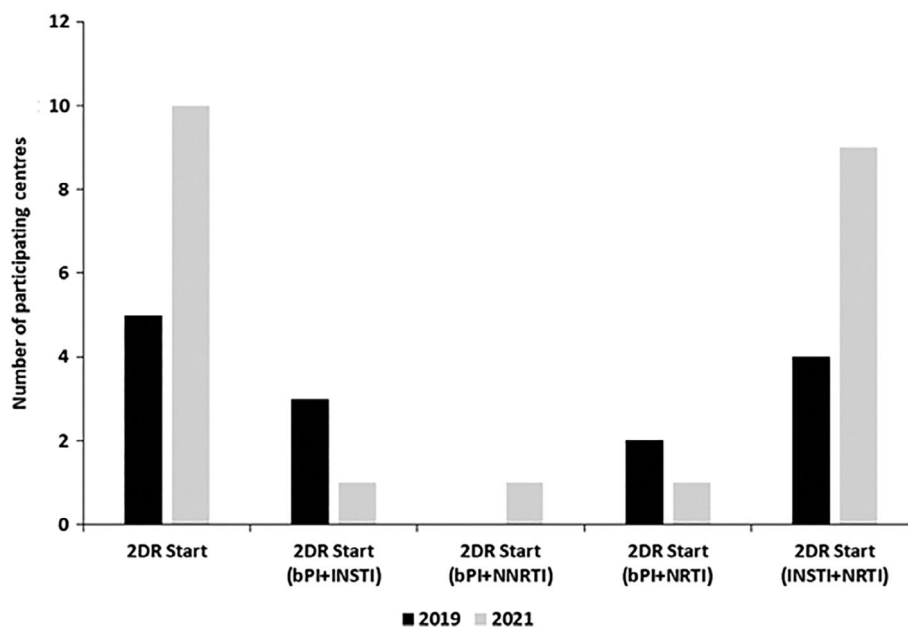


FIGURE 1 Trends in 2DR initiation between 2019 and 2021 (total and according to 2DR regimen). 2DR, two-drug regimen; bPI, boosted protease inhibitor; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor

TABLE 1 Reasons for initiating two-drug regimens

Reason	2019				2021			
	Central	Eastern	South Eastern	Total (n, %)	Central	Eastern	South Eastern	Total (n, %)
Metabolic disorders	1	1	3	5 (28)	1	1	3	5 (28)
Adverse drug reactions	0	2	1	3 (16)	1	2	1	4 (22)
Viral load <500 000 c/ml with high CD4 count	0	0	1	1 (6)	4	1	3	8 (44)
Others (simplicity, tolerability, efficacy, CKD)	0	2	1	3 (16)	1	2	3	6 (33)

Abbreviations: CD4, cluster of differentiation; CKD, chronic kidney disease.

The number of participants reporting switching ART to 2DR remained relatively constant ($n = 15$ [83%] in 2019 vs $n = 14$ [78%] in 2021). An INSTI/NRTI combination was the most commonly used 2DR in both evaluations (80% and 93%, respectively). Prescriptions of boosted PI/INSTI decreased from 60% to 36% and prescriptions of boosted PI/NRTI decreased from 53% to 21%.

The main reasons that promoted ART switching to 2DR in the first and second evaluation were metabolic disorders, e.g. dyslipidaemia, insulin resistance (61% vs 50%) and adverse drug reactions (72% vs 56%), and treatment failure (28% vs 6%).

Differences were also observed between regions in the implementation of 2DR for ART start and switching. Specifically, among the four CE centres, 2DR ART initiation increased from only one in 2019 to four in 2021. We also found a similar, although modest, increase among the eight SEE centres (from one to three). In contrast with these two regions, the number of EE centres using 2DR for this indication declined from three to two (in a total of six). An INSTI/NRTI combination was the most commonly prescribed ART for 2DR treatment initiation in all regions in the second evaluation. Of note, the centres in the SE region were using only the INSTI/NRTI combination in both surveys. No noteworthy differences in the patterns of 2DR prescription for ART switching were noted among regions between the two time points. All four centres in CE, five of six in EE and five of eight in SEE were using 2DR for switching in 2021.

DISCUSSION

In our 2019 and 2021 studies, we observed widespread introduction of modern antiretrovirals and new treatment strategies among the majority of represented countries, except for the EE countries. The use of novel antiretroviral drugs such as newer INSTI and TAF has

been associated with strong viral suppression, better tolerance, reduced viral resistance, fewer adverse events and fewer drug–drug interactions [10–12]. In addition, FDCs are correlated with better adherence to therapy. As a result, the use of these drugs is deemed necessary to achieve the UNAIDS third goal of 95-95-95, and most of the aforementioned drugs are now considered as first-choice drugs in international guidelines [10–12].

Until a few years ago, the availability of the newer drugs and FDC was low in CE countries and especially in EE countries [5]. In a 2015 survey of 22 CE and EE countries, the availability of older antiretroviral drugs or regimens (e.g. ZDV, 3TC, abacavir [ABC], ZDV/3TC, TDF/FTC [91.7% each], TDF [83.3%], LPV/r [95.8%], DRV [79%] and RAL [70.8%]) was high. Novel combinations were poorly available, especially in EE (e.g. DRV/c [16.7%], ELV/c/FTC/TDF [20.8%] and DTG/ABC/3TC [20.8%]) [4]. Although these data are only partially comparable with our own survey (since the number of countries and centres differs), it is obvious that the current situation has notably improved compared with not only 2015 but also 2019. By 2021, all modern antiretroviral regimens with TAF, DRV/c and BIC had been introduced and are increasingly available, and regimens with TDF/FTC, ABC/3TC, DRV/r, DTG and RAL are broadly available. During this period, the use of older drugs decreased, and some, such as SQV, have been almost withdrawn.

This increased drug availability in most countries (especially in CE and SEE) indicates the possibility of strong harmonization with the most recent EACS and international guidelines and constitutes a strong springboard to fulfilling the target of complete and prolonged viral suppression. The situation in EE countries has improved but is not yet ideal, since some regimens including TAF and BIC are not available and ELV/c/FTC/TAF is underrepresented.

It is necessary to explore the factors that affect the availability of current drugs (e.g. bureaucracy, finances,

national guidelines that do not support their use) and make efforts to overcome these obstacles with a goal of alignment between the region and the rest of Europe [6].

A remarkable finding of our study is that ART delivery was not significantly interrupted in most centres during the COVID-19 pandemic. Only a few transient delays or switches in ART were noted. This study confirms recent reports from CE and EE, where HIV clinics continued to function during the first wave of the COVID-19 pandemic despite various difficulties or reduced staff. Nevertheless, ART distribution was not remarkably affected and, in most countries, these drugs were dispensed for 2–6 months [13].

In 2017, the World Health Organization (WHO) launched guidelines on the management of advanced HIV disease and rapid initiation of ART and suggested that all people living with HIV should start ART within ≤ 7 days of a positive HIV diagnosis, even on the same day for people who are ready to start [14]. Various studies have demonstrated that immediate or early access to ART within days or a few weeks after HIV diagnosis results in rapid and likely virological suppression, greater CD4⁺ T-cell increases, decreased sexual and perinatal transmission and higher linkage to care [15, 16]. The WHO recommendations have been endorsed by EACS and international guidelines (US Department of Health and Human Services, International Antiviral Society-USA) [10–12].

It was noteworthy that half of the centres in all regions of our survey had already implemented the rapid ART start strategy just 2 years after the WHO recommendations, and this proportion increased to two-thirds of the centres within another 2 years. This strategy was offered mainly to pregnant women but also to vulnerable populations, such as the active PWID and MSM with high-risk sexual behaviours to improve linkage to care. It is also of interest that the attending physicians take under serious consideration social factors such as living a long distance from a clinic or financial difficulty covering travel expenses to rapidly offer ART. The most frequently administered antiretroviral drugs were the INSTI-based regimens in EE and exclusively in SE, whereas PI-based regimens are preferred in CE. Both regimens possess a higher barrier to resistance, which is crucial in regions where resistance testing is not easily or immediately available [4, 6, 16, 17]. Current guidelines recommend the use of triple INSTI (DTG or BIC)-based or PI (DRV)-based regimens when ART is being initiated rapidly before HIV drug resistance results are obtainable [10–12]. These guidelines also recommend that DRV-based regimens are used as alternative options or in certain clinical situations. Therefore, it is reasonable that our survey noted a tendency for the more frequent use of INSTI-based regimens (especially in SEE).

The main obstacles for rapid ART start in both time points were national guidelines that did not support this strategy or that required resistance test results before starting ART. In a previous survey of countries in the region, 25% of respondents were updating their national guidelines every 4 or 5 years, and clinicians were totally adherent to guideline recommendations [4]. Nevertheless, as stated, two-thirds of the centres are already providing rapid ART, and it is anticipated that the rest will encompass the EACS or international recommendations within their own national guidelines.

The use of 2DR for initial or maintenance treatment in people living with HIV has challenged traditional three-drug therapies because of the potential to reduce adverse effects, drug interactions and cost [18, 19]. The EACS guidelines were the first to recommend the 2DR DTG/3TC for consideration as a first-line regimen for treatment-naïve patients, excluding patients with hepatitis B, high HIV-1 RNA $>100\,000$ c/ml and a CD4 count <200 cells/mm³ [10]. Other international guidelines endorsed this recommendation [11, 12]. Other 2DR combinations (e.g. RAL + DRV/r(c), DRV/r + 3TC, LPV/r + 3TC) were recommended in the guidelines as alternative regimens with certain restrictions in particular clinical situations or when first-line regimens were not feasible [10–12].

Although a 2014 survey of 22 countries in CE and EE found no 2DR as a first-line combination, our 2019 survey found that 28% of the centres in the region were already using a 2DR regimen for initial ART [4]. Most importantly, in just 2 years this proportion doubled (55%) and there was a shift towards using the INSTI/NRTI combination more frequently (75%) and exclusively in SEE. It is interesting that metabolic disturbances and adverse drug reactions were the main reasons to prefer a 2DR for starting ART in 2019; in 2021, almost half of the centres mentioned only lower viral load and a high CD4⁺ count as prerequisite for the adoption of this strategy. This implies that physicians in the region are increasingly accepting the current European and national guidelines to initially offer a 2DR for simplicity, tolerability, avoidance of adverse reactions and lower cost, while at the same time preserving efficacy.

In the past decade, multiple studies have shown that several 2DRs containing drugs from all main antiretroviral classes could be used as maintenance or switch ART replacing the traditional triple combinations. These 2DR regimens have been incorporated as alternative options in the guidelines [10–12, 19]. The first 2DR to be used were the combinations of bPI + NRTI [LPV/r + 3TC, ATV/r(c) + 3TC, DRV/r(c) + 3TC], INSTI + NNRTI [DRV/r(c) + rilpivirine] and INSTI + bPI [DTG + DRV/r(c)], whereas INSTI + NRTI (DTG + 3TC) was added

later. As such, it is no surprise that most centres in our survey were using various 2DR for switching ART, and the percentage did not essentially change in both evaluations. The INSTI + NRTI combination was the most commonly used following the general trend of replacing the other 2DR with this one. This trend was probably based on the appearance of robust studies that support this choice [20]. It is also quite plausible that the main reasons for switching were also metabolic disorders and drug adverse events. In the second survey, treatment failure was almost eliminated as a reason to switch, which reflects the fact that current antiretroviral regimens have a very favourable resistance profile and that drug tolerability substantially improved adherence [21].

This study has several limitations. This is a cross-sectional survey study where each country was represented by only one (or two) centres, so it may not reflect the exact situation of HIV infection in each country. However, each country was represented by a major centre with nationally recognized experts in the field who have been actively involved in patient care in their countries and have provided as accurate as possible data [7]. Centres represented in the survey have a long ongoing collaboration since 2016 and represent the standard of care provided in their country. Of note, some countries such as Croatia have only one centre because it is a low-incidence region. Another limitation is that limited or no data are given concerning NNRTIs, and certain questions did not describe the antiretroviral combinations in detail.

In conclusion, over the past few years, in spite of the emergence of the COVID-19 pandemic and many physicians being involved in the management of patients with COVID-19, significant achievements concerning ART availability and strategies have taken place in CE, EE and SEE. All novel ART drugs are now available, with few exceptions, mostly in EE. This drug availability facilitates the harmonization of ART with EACS guidelines. New ART strategies such as rapid ART start and 2DR in ART start and switch are gaining ground in daily practice. Continuous efforts, such as those undertaken by the ECEE Network Group, are needed to overcome various obstacles (administrative, funding, national guidelines, novel drug availability, etc.) in some countries. Most importantly, ART achievements are expected to improve the cascade of care in the region.

AUTHOR CONTRIBUTION

JDK, ASK and AH conceptualized the survey design, conducted the online survey and collected data from all centres. AP, KP, SA, JB, GD, DG, KK, VK, BL, MM, RM, VM, CO, AP, DS, LS, ASK, AV, NY, OY and JDK collected data in each participating centre. AP, KT and KP

analysed the data. AP and KT drafted the manuscript. AP, KT and JDK critically revised the manuscript.

ACKNOWLEDGEMENTS

This study was supported by an unrestricted research grant from the Foundation of Research Development in the Hospital for Infectious Diseases, Medical University of Warsaw, Poland.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest relevant to this work.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

PATIENT CONSENT STATEMENT

Since this study does not include individual patient data, it does not include factors necessitating patient consent.

ORCID

Cristiana Oprea  <https://orcid.org/0000-0001-9581-2527>

Agata Skrzat-Klapaczyńska  <https://orcid.org/0000-0002-6367-5633>

Justyna D. Kowalska  <https://orcid.org/0000-0003-1166-4462>

REFERENCES

- 2021 UNAIDS Global AIDS Update—confronting inequalities—lessons for pandemic responses from 40 years of AIDS. Accessed 3 April 2022. <https://www.unaids.org/en/resources/documents/2021/2021-global-aids-update>
- Gourlay AJ, Pharris AM, Noori T, et al. Towards standardized definitions for monitoring the continuum of HIV care in Europe. *AIDS*. 2017;31(15):2053-2058. doi:10.1097/QAD.0000000000001597
- UNAIDS. Understanding fast-track: accelerating action to end the AIDS epidemic by 2030. 2020. Accessed 8 August 2022. [unaids.org/sites/default/files/media_asset/201506_JC2743_Understanding_FastTrack_en.pdf](https://www.unaids.org/sites/default/files/media_asset/201506_JC2743_Understanding_FastTrack_en.pdf)
- Gokengin D, Oprea C, Begovac J, et al. HIV care in central and Eastern Europe: how close are we to the target? *Int J Infect Dis*. 2018;70:121-130. doi:10.1016/j.ijid.2018.03.007
- De Wit S, Battegay M, D'Arminio Monforte A, et al. European AIDS clinical society second standard of care meeting, Brussels 16–17 November 2016: a summary. *HIV Med*. 2018;19(2):77-80. doi:10.1111/HIV.12559
- Brown AE, Hayes R, Noori T, et al. HIV in Europe and Central Asia: progress in 2018 towards meeting the UNAIDS 90-90-90 targets. *Euro Surveill*. 2018;23(48):1. doi:10.2807/1560-7917.ES.2018.23.48.1800622
- Kowalska JD, Oprea C, de Witt S, et al. Euroguidelines in central and Eastern Europe (ECEE) conference and the Warsaw declaration—a comprehensive meeting report. *HIV Med*. 2017; 18(5):370-375. doi:10.1111/HIV.12436

8. Balayan T, Oprea C, Yurin O, et al. People who inject drugs remain hard-to-reach population across all HIV continuum stages in central, eastern and South Eastern Europe—data from euro-guidelines in central and Eastern Europe network. *Infect Dis (Lond)*. 2019;51(4):277-286. doi:10.1080/23744235.2019.1565415
9. Miles to go—Global AIDS update 2018. Accessed 3 April 2022. https://www.unaids.org/en/20180718_GR2018
10. EACS guidelines. Accessed 3 April 2022. <https://www.eacsociety.org/guidelines/eacs-guidelines/>
11. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Accessed 3 April 2022. <https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf>; <http://hivinfo.nih.gov>
12. Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the international antiviral society-USA panel. *JAMA*. 2020;324(16):1651-1669. doi:10.1001/JAMA.2020.17025
13. Kowalska JD, Skrzat-Klapaczyńska A, Bursa D, et al. HIV care in times of the COVID-19 crisis—where are we now in central and Eastern Europe? *Int J Infect Dis*. 2020;96:311-314. doi:10.1016/J.IJID.2020.05.013
14. World Health Organization. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Published 2017. Accessed 3 April 2022. <https://www.who.int/publications/i/item/9789241550062>
15. Boyd MA, Boffito M, Castagna A, Estrada V. Rapid initiation of antiretroviral therapy at HIV diagnosis: definition, process, knowledge gaps. *HIV Med*. 2019;20(Suppl 1):3-11. doi:10.1111/HIV.12708
16. Michienzi SM, Barrios M, Badowski ME. Evidence regarding rapid initiation of antiretroviral therapy in patients living with HIV. *Curr Infect Dis Rep*. 2021;23(5):7. doi:10.1007/S11908-021-00750-5
17. Boucher CA, Bobkova MR, Geretti AM, et al. State of the art in HIV drug resistance: science and technology knowledge gap. *AIDS Rev*. 2018;20(1):27-42.
18. Waters L, Church H. Two drugs regimens for HIV. *Curr Opin Infect Dis*. 2020;33(1):28-33. doi:10.1097/QCO.0000000000000615
19. Badowski M, Pérez SE, Silva D, Lee A. Two's a company, Three's a crowd: a review of initiating or switching to a two-drug antiretroviral regimen in treatment-Naïve and treatment-experienced patients living with HIV-1. *Infect Dis Ther*. 2020;9(2):185-208. doi:10.1007/S40121-020-00290-W
20. Van Wyk J, Ajana F, Bisshop F, et al. Efficacy and safety of switching to Dolutegravir/lamivudine fixed-dose 2-drug regimen vs continuing a Tenofovir Alafenamide-based 3- or 4-drug regimen for maintenance of Virologic suppression in adults living with human immunodeficiency virus type 1: phase 3, randomized, noninferiority TANGO study. *Clin Infect Dis*. 2020;71(8):1920-1929. doi:10.1093/CID/CIZ1243
21. Mbhele N, Chimukangara B, Gordon M. HIV-1 integrase strand transfer inhibitors: a review of current drugs, recent advances and drug resistance. *Int J Antimicrob Agents*. 2021;57(5):106343. doi:10.1016/J.IJANTIMICAG.2021.106343

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Papadopoulos A, Thomas K, Protopapas K, et al. HIV treatment strategies across Central, Eastern and Southeastern Europe: New times, old problems. *HIV Med*. 2023; 24(4):462-470. doi:10.1111/hiv.13416