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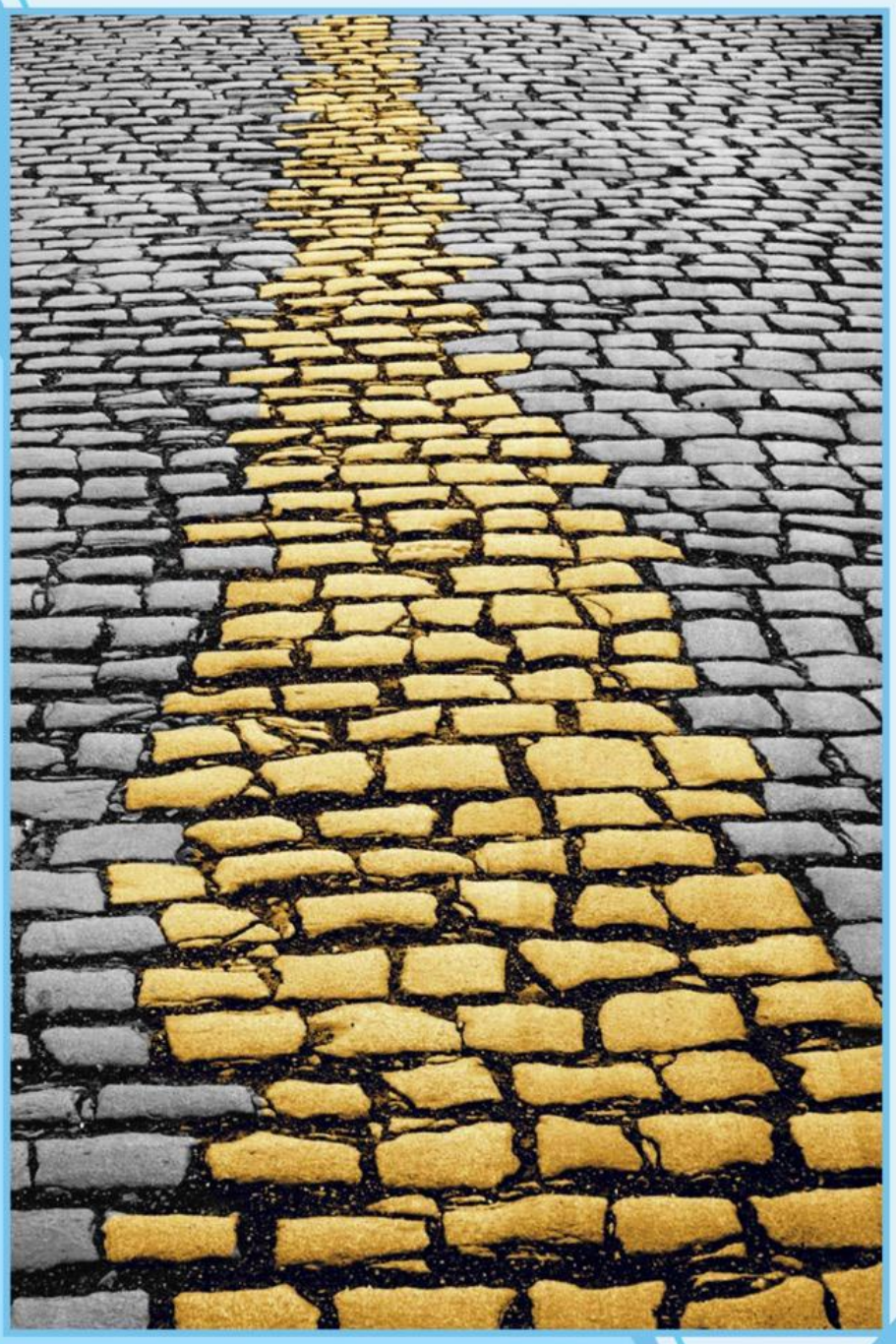
International Treatment Preparedness Coalition
Eastern Europe and Central Asia

On the way to 90

Analysis of procurement and provision of ARV drugs in seven countries of Eastern Europe and Central Asia



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Contents

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Mentioning of any international nonproprietary names or trade names of drugs does not mean that the authors of the report give them preference or, on the contrary, do not recommend them.

Mentioning of any treatment regimens in the text of this report under no circumstances can be used as an alternative to consulting with a medical specialist.

Abbreviations

ARV	– antiretroviral
WHO	– World Health Organization
DMP	– Department of medicines provision
EEU	– Eurasian Economic Union
VED	– Vital and Essential Drugs
II	– Integrase inhibitors
PI	– Protease inhibitors
KR	– Kyrgyz Republic
VAT	– Value Added Tax
NRTI	– Nucleoside Reverse Transcriptase Inhibitor
non-NRTI	– Non-Nucleoside Reverse Transcriptase Inhibitor
NGO	– Non-Governmental Organization
LLEMP	– List of Life-Saving and Essential Medicinal Products
MA	– Marketing Authorization
FDC	– Fixed Dose Combination, combination drug
UNAIDS	– Joint United Nations Program on HIV/AIDS
ABC	– abacavir
ATV	– atazanavir
AZT	– zidovudine
BIC	– bictegravir
DRV	– darunavir
DTG	– dolutegravir
EFV	– efavirenz
EVG	– elvitegravir
LPV	– lopinavir
NVP	– nevirapine
RAL	– raltegravir
RIL	– rilpivirine
/r	– ritonavir
/c	– cobicistat

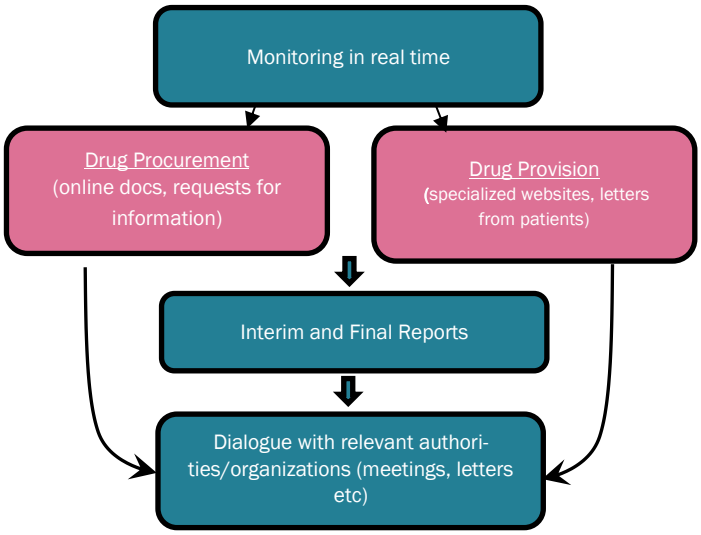
Introduction

In 2010, patients in Russia experienced massive disruptions in the provision of antiretroviral drugs for HIV infection treatment. These disruptions were so large-scale and obvious that, as a result, even the Procurator General's Office of the Russian Federation, as reported on the web-site of the agency, identified "numerous violations in the procurement [*by the Ministry of Health of the Russian Federation*] of diagnostic tools and antiviral drugs."

Patients responded to the disruptions with protest campaigns, letters and appeals to the Ministry of Health, regulatory authorities and mass media. This situation once again showed how important it is for the patient community to have an established system that allows to monitor and analyze the entire chain of manufacturer-to-patient movement of drugs.

The protest at the Ministry of Health, 2010. Photo by pereboi.ru (Signs say "We are tired of your farce")

This system was built gradually, starting with tools that allowed tracking and solving problems in real time: websites for reporting disruptions (for example, pereboi.ru) and so-called "ARV emergency stocks" that allow patients to exchange drugs in emergency cases. However, in order to effectively and, most importantly, comprehensively resist the shortage of drugs and the refusals to issue them, the system needed to be expanded. Having analyzed the situation, patient organizations identified the relationship between disruptions and the peculiarities of the procurement procedure and the provision of ARVs implemented in Russia. In order to understand the problem in detail, in 2010 the International Treatment Preparedness Coalition, together with representatives of the Patient Control movement, launched a project on *monitoring and analyzing procurement of antiretroviral drugs*. In 2011, this project spread to the procurement of drugs for the treatment of viral hepatitis C *(HCV)*. The first results of the analysis were published in the Alternative Report "Russia is halfway to universal access: between power and the epidemic" in 2011. In 2013, based on the accumulated experience, in collaboration with E.V.A. non-profit partnership, the first analysis of the procurement of drugs for the treatment of *tuberculosis* was conducted.



During the nine years of the project (from 2010 to 2018), the Treatment Preparedness Coalition annually published interim and final annual monitoring reports. Analytical data, conclusions and recommendations, as well as operational data on drug provision disruptions and other problems were repeatedly presented at meetings with the government, expert meetings, conferences, used in writing appeals and inquiries, and quoted in the media. Frequent attention to the overpricing of drugs, among other things, has led the Russian government to systematically draw their attention to the need to lower prices and expanding access to therapy. Changes (or proposals

for change) were made to the regulatory framework: in particular, in the field of price registration for generic drugs (generics), the development of competition in the drug market in general, compulsory licensing for public healthcare, etc.

In 2016, the International Treatment Preparedness Coalition decided to spread out their experience in drug procurement monitoring in the countries of Eastern Europe and Central Asia (EECA). The first step was to issue at the end of 2016 a report on registration status, procurement mechanisms and prices of ARV drugs in the countries of the Eurasian Economic Union. In 2017, due to the increased interest in this topic, monitoring of the access to drugs was expanded, and the new project, which was supported by the UNAIDS regional office for EECA countries, included Moldova and Ukraine, in addition to the EEU countries. Earlier, during 2015-2016 with technical support from the Coalition in several EECA countries, websites were created to collect operational information about disruptions in the provision of drugs: Belarus (pereboi.by), Kazakhstan (pereboi.kz), Moldova (pereboi.md), Kyrgyzstan (pereboi.kg) .

As a part of the project, in seven countries of the region (Armenia, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Russia and Ukraine) patient organizations analyzed the latest available data on procurement of ARVs, epidemiology, regulatory framework, registration and patent status of drugs. They summarized the results and presented them in the form of national reports containing conclusions and recommendations on how to improve access to therapy. Later on, these conclusions and recommendations were discussed at meetings with officials, politicians, employees of international agencies, at national and international conferences and in the media.

The regional report contains a summary of the analysis of procurement of ARV drugs in all seven countries. The authors of this report hope that it will serve as a basis for further activities to improve the availability of ARV therapy in the EECA region, as well as to expand the project to other diseases, primarily tuberculosis and viral hepatitis B and C. **The authors of this report also point out that all detailed information about the situation in the seven countries is included in the national reports.**

Links to national reports (in Russian):

Armenia: “Monitoring procurement of drugs for treating HIV infection and making decisions on how to optimize the situation in order to facilitate uninterrupted access to drugs in the Republic of Armenia, 2017”

Belarus: “Provision of antiretroviral drugs in the Republic of Belarus and the possibility of its optimization”

Kazakhstan: "Study on the procurement of antiretroviral drugs for the treatment of HIV infection in 2017 in the Republic of Kazakhstan"

Kyrgyzstan: “Analysis of procurement of antiretroviral drugs in Kyrgyzstan in 2017”

Moldova: "Monitoring the procurement of drugs for treating HIV infection. Solutions to optimize the situation in order to facilitate uninterrupted access to drugs in the Republic of Moldova"

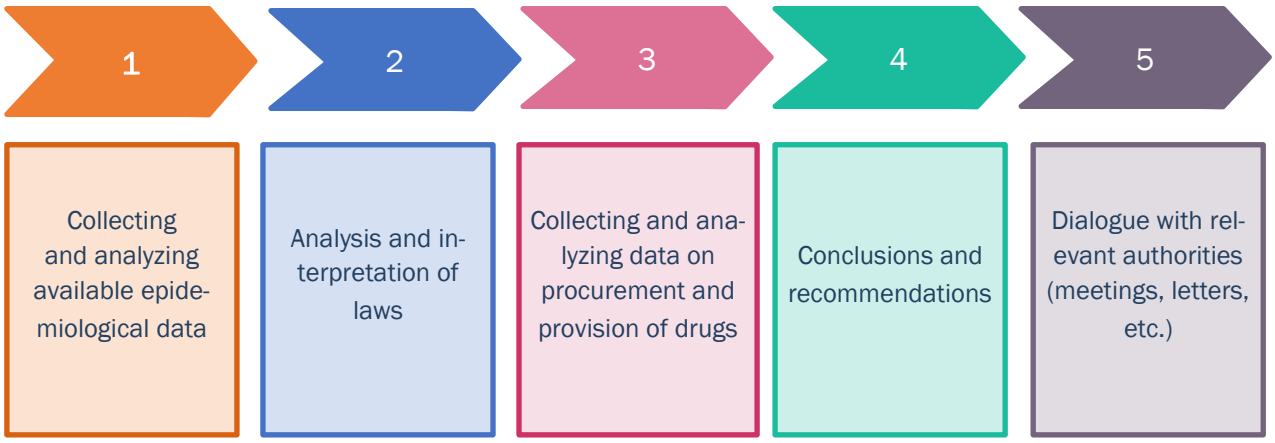
Russia: “Expanding coverage: risks and opportunities. Results of monitoring the procurement of ARV drugs in 2017 "

Ukraine: "Report on the results of monitoring the procurement of ARV drugs in Ukraine"

Project Implementation

The project was implemented in two stages. According to the concept, partner organizations in countries at the first stage were to prepare a *document* summarizing the data on the HIV treatment situation in the country, with a focus on the results of procurement analysis of ARV drugs for the last year (preferably 2017). Based on the results of the analysis, it was necessary to offer recommendations aimed at improving the access of HIV positive people to therapy. Further, this document should have been presented to relevant institutions, i.e. ministries of health, republican AIDS centers, international procurement agencies (UNDP, UNICEF, Global Fund), national procurement agencies, and outline the areas for joint work on improving access to ARV therapy in the future. For this purpose, *special events* were organized within the project; in addition, the results of the analysis were presented at side events (national conferences, meetings of partner projects, etc.).

The framework for the report had been developed in advance, based on previously written reports on this topic and approved with the project participants and UNAIDS. It included several sections, described below.



Analysis of the epidemiological situation. It was proposed to include in the report the information on the most frequently used epidemiological indicators characterizing the state of the HIV epidemic in the country: the absolute number of people, prevalence, incidence and mortality rate caused by the disease. These are basic statistics that are important for assessing the situation with the epidemic in general and the need for ARV therapy in particular.

In addition, it was recommended to pay attention to the number of people already receiving antiretroviral therapy, and the number of people in need of antiretroviral therapy. For evaluation, it was offered to use the *treatment cascade* system: the percentage of people registered of the estimated number of people with HIV, the percentage of people receiving therapy of the number of registered, the percentage of people with undetectable viral load. The regional report contains a section with data on the treatment cascades in seven countries.

Analysis of legislation concerning the procurement and provision of ARVs. It was proposed to analyze the laws and regulations governing the response to the epidemic of HIV infection, the budget allocated for the procurement of drugs for the treatment of HIV infection, procedures for registering funds, procedures for procurement of drugs, restrictive lists, including lists of vital and essential drug products or lists of drugs to be procured. It was proposed to include in the reports the lists of ARV drugs registered in the countries, as well as the analysis of national recommendations on the treatment of HIV infection, with a focus on their compliance with current international recommendations. When analyzing the protocols, special attention was paid to the preferred and alternative treatment regimens, as well as the criteria for prescribing therapy.

In analyzing of the legislation, it was recommended that special emphasis should be placed on the possibilities and barriers to procurement of drugs through international agencies. The hypothesis that was planned to test was that procurement with the involvement of international agencies is a more economical way for countries with small budgets that are in the process of transition from donor to public funding rather than procurement by national agencies.

Analysis of procurement and provision of antiretroviral drugs in 2017. The following parameters were proposed, among other things, to be included in the analysis:

- The total amount of finances allocated and spent for the procurement of ARV drugs, as well as funding sources (state budget, Global Fund to Fight AIDS, Tuberculosis and Malaria, PEPFAR, etc.).
- The procurement mechanisms (national procedures, procurement through international agencies, drug donations) used.
- The list of procured products with indication of the international non-proprietary name (INN), trade name (TN), dosage, drug dosage form, procurement quantity (tablets, packages).
- Cost analysis of each individual drug in absolute numbers and as a percentage of the total budget.
- Analysis of prices for each drug product (per unit, per package, per patient a year). If there are several auctions, the calculation of the minimum/maximum/weighted average prices (relevant for countries with a large number of tenders, for example, Russia) must be carried out.
- Analysis of the main treatment regimens and calculation of the number of patients on therapy based on monitoring results.
- Comparison of procured treatment regimens with national and international guidelines for treating HIV infection.
- Analysis of available information about disruptions in the provision of drugs to patients (data from specialized websites, patient forums, personal appeals to organizations, etc.).

Conclusions and recommendations on the results of the analysis. In this section, it was proposed to include, among other things, the information on the estimated number of people receiving therapy and those in need of treatment, as well as the comparison with official data (if available), main treatment regimens, drugs being the largest share in the budget, prices of the first and second line regimens, the possibility of transition to new ARV drugs. Key recommendations should include:

- Recommendations in the field of optimization of the procurement process, analysis of legislative barriers and ways to eliminate/mitigate them.
- Recommendations for increasing the number of patients receiving therapy.
- Recommendations in the field of improving the nomenclature (alignment with international recommendations, etc.).

- Recommendations in the field of reducing prices for specific drugs products.

From October 2017 till May 2018, partners in the countries prepared seven reports covering the situation with HIV treatment, with recommendations on how to improve access to therapy. Later, in each of the countries, meetings were held to discuss the results of the report and develop a further working strategy. The list of participants varied from country to country.

Report presentation in Kyrgyzstan, February 2, 2018

For example, in Kyrgyzstan on February 2, 2018, a roundtable meeting was held, which was attended by deputies, representatives of the Government staff, the Minister of Health of the Kyrgyz Republic, the chairman and representatives of the Mandatory Medical Insurance Fund, representatives of the Department of Drug Support (DDS), heads of medical institutions, representatives of international organizations, NGO leaders and experts. The results of the study were announced and questions were asked to the representatives of the DDS, how it would be possible to improve the situation in the country on the availability of ARV drugs in the Kyrgyz Republic. In particular, issues related to the adoption of a new List of Life-Saving and Essential Medicinal Products (LLEMP) were raised. It is important to point out that the analysis revealed the situation with the procurement of drugs at inflated prices. In this regard, the Partnership Network Association (the organization that implemented the project) held talks with UNDP, UNICEF and the Patent Pool of drug products. At present, further actions are planned aimed at reducing the prices of drugs with unreasonably high prices.

In Moldova, the results of the study, among other things, were presented at the 4th National Conference on HIV/AIDS (2017), as well as at the working meeting of representatives of patient organizations with the UNDP team in Moldova in relation to health needs, a working meeting at the Parliamentary Commission on public health and social protection, an expanded meeting of the Committee of HIV Vulnerable Communities and at a roundtable meeting on intellectual property and access to medicines (Chisinau, March 21, 2018), which took place with the participation of representatives of the Ministry of Health.

National Conference on HIV Infection in Moldova

Special events to discuss the results of the projects were held in Belarus, Kazakhstan, Ukraine and Armenia. In Kazakhstan, following the meeting organized by the national office of UNAIDS, a resolution was drawn up with a list of specific measures needed to improve the availability of ARV therapy (in particular, the need to reduce prices in the framework of national procurement was mentioned). The resolution, signed by the participants of the meeting, was sent to the Ministry of Health, whose response is expected. The implementa-

tion of the recommendations of the report is in progress, including the meetings with the Ministry of Health, letters to the antimonopoly service, and publications in social networks.

A special technical meeting was held in Belarus with the participation of representatives of the Ministry of Health, at which an action plan was developed based on the results of the analysis. The text of the plan, as well as a description of the consultation procedure, are provided in the national report (see pages 70-72) as a separate section.

The discussion of the results of ARV drugs procurement analysis in Ukraine

The summary data on prices, volumes and procurement structure were presented at the 6th AIDS Conference in Eastern Europe and Central Asia, which was held in Moscow from April 18 to April 20. A separate presentation was devoted to the results of the analysis of procurement of ARV drugs in the Russian Federation. Also, according to the results of the Russian report, a letter was sent to the Ministry of Health with a call to take measures to reduce the prices of patented clinically significant drugs.

Report presentation in Kazakhstan

Detailed recommendations for improving of the access can be found in the country report texts. Since recommendations in each country were discussed with officials, they will serve as a basis for coordinated actions of public organizations and governments at the national level. A common regional drug-specific strategy is planned to be discussed as part of regional treatment access initiatives, such as the Eurasian Community for Access to Treatment (ECAT).

Epidemiology in EECA

The scope statement for the national reports included a set of questions, which was conventionally called *epidemiological set of questions*. As a result, the national reports (to a greater or lesser extent) accumulated detailed information on the basic indicators characterizing the development of the epidemic: prevalence among the general population and among key groups, incidence (number of new cases per unit of time), mortality rate, etc.

Since the project was mainly focused on monitoring and improving the access to therapy, in the regional summary report, the authors decided to focus on a set of indicators called the *treatment cascade*. It was used by UNAIDS in developing the 90x90x90 strategy, which today is adapted by many governments and is the foundation of national strategies to fight HIV infection.

The treatment cascade in its basic form consists of four indicators:

- The estimated number of people living with HIV infection.
- The number of people who are aware of their status (the goal is 90 percent of the estimated number of people with HIV infection).
- The number of people who receive ARV therapy (the goal is 90 percent of the number of people who are aware of their status).
- The number of people with suppressed viral load (the goal is 90 percent of the number of people receiving ARV therapy).

The main goals of therapy:
- to increase in the duration and retain (improve) of the quality of human life
- to reduce the risk of transmission of HIV

These goals are achieved by maximizing the reduction in viral load in the blood, ideally to an undetectable level.

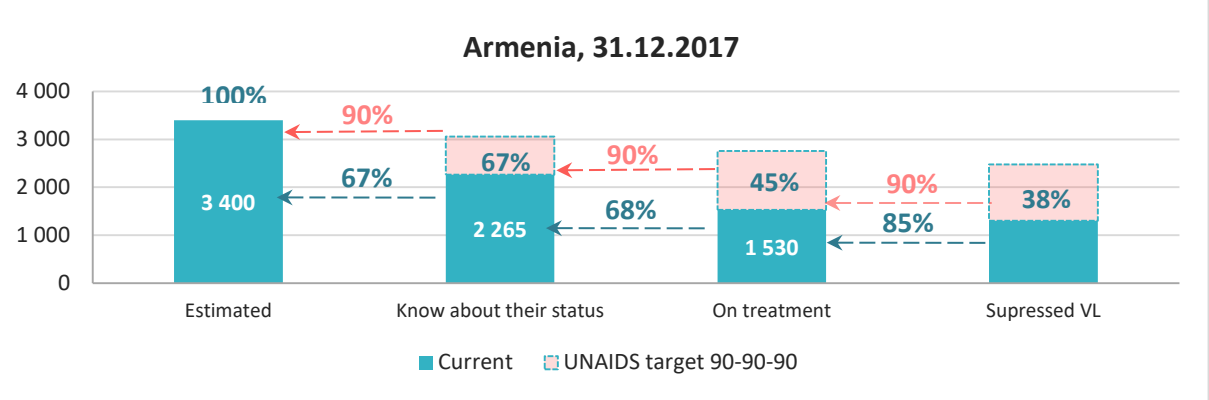
Below are the graphs depicting treatment cascades in each of the countries where the study was conducted. To make them easier to analyze, it is important to give some explanations. The graphs show two sets of indicators. The first is the “classic” 90x90x90, where each indicator is calculated from the previous one. In order to obtain an effective response to the epidemic, it is important that all three indicators are achieved together. In the second set of indicators, the basis for calculating all subsequent indicators is the estimated number of people with HIV infection. It is convenient to use in order to estimate what percentage of HIV-positive people have a suppressed viral load and, as a result, can live a full life without transferring the virus to others. Accordingly, their target percentages will be slightly different: 90, 81 and 73 percent.

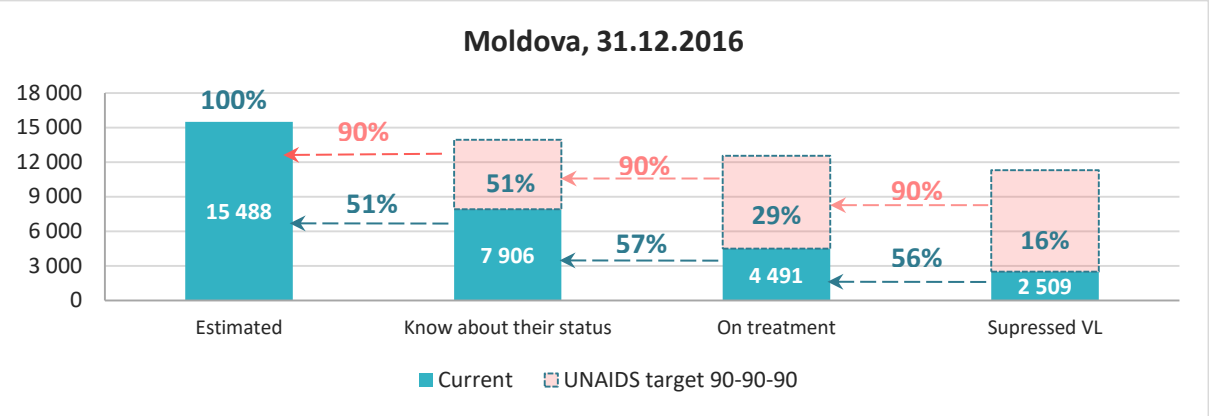
The first indicator in the graphs (the percentage of people who know their status, of the total estimated number of people) is the same in both sets of indicators; therefore, it is represented by the percentage at the top of “who are aware of their HIV status” column. Further, the percentages associated with the 90x90x90 indicator set are presented in the form of gray dotted arrows leading to the previous column. Indicators that are calculated from the total estimated number of people are represented by percentages above the green bars.

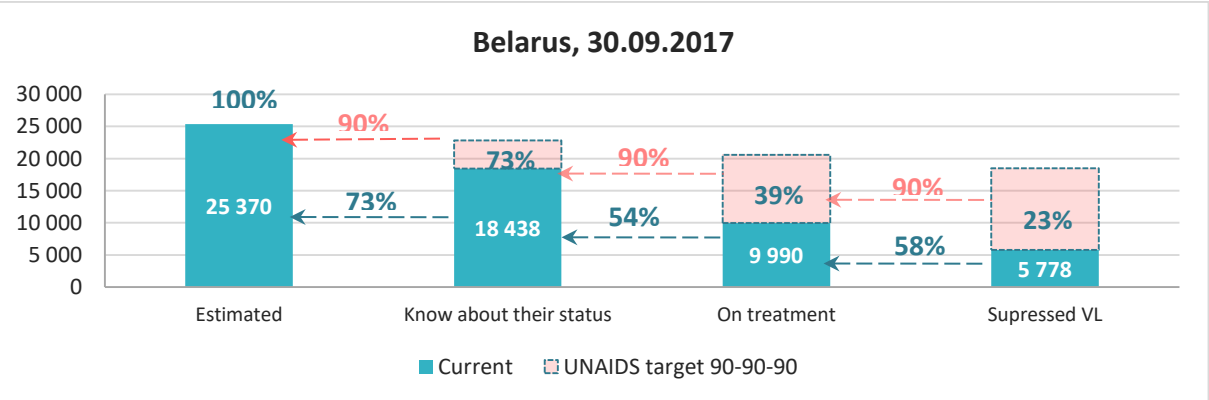
To make the picture complete, it is important to use both sets of indicators. For example, in one country there may be 90 percent of people with suppressed viral load from the number of people receiving ART, but 50 percent of the number of people who know their status, and the group with suppressed VL is only 30 percent from the total estimated number of people.

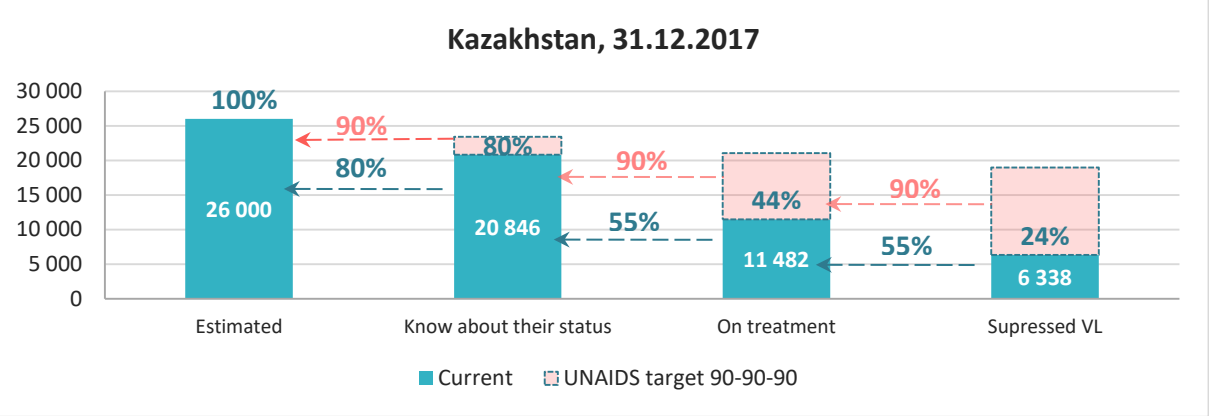
These numbers may indicate that ARV therapy is effective, but considerable work is still required to increase the number of patients receiving ART.

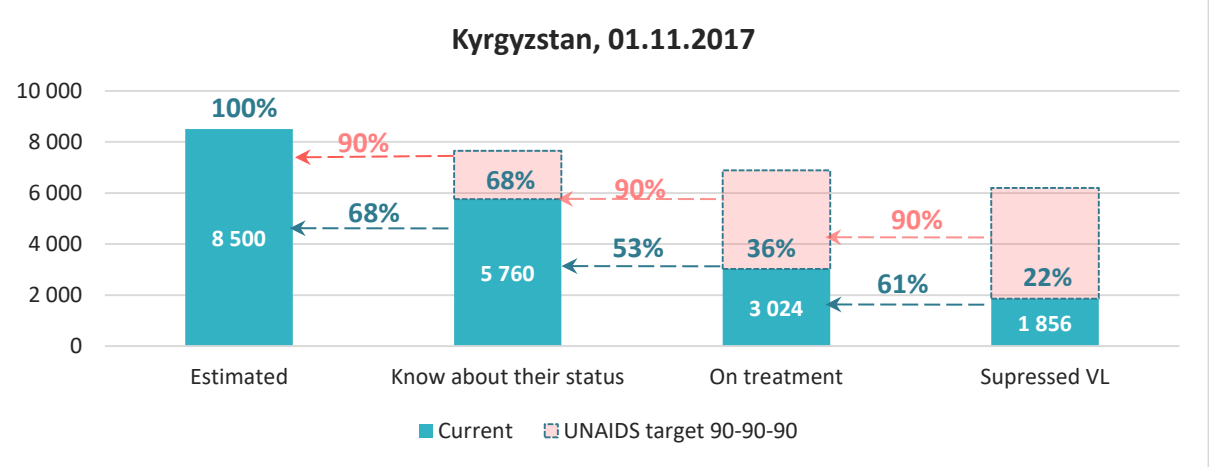
In none of the seven countries where the study was conducted, the indicators of the treatment cascade reach either 90x90x90 or 90x81x73. Armenia, judging by the data provided, is close to reaching the "third" 90 percent (which is the percentage of patients with suppressed VL of the number of people on ART), and is relatively close to achieving the first two indicators. Belarus and Kazakhstan are relatively close to achieving the "first" 90 percent (the percentage of people who know their status, of the total estimated number of people). In all countries, the percentage of people with suppressed VL of the total estimated number of people with HIV infections is critically low. With the exception of Armenia (38 percent), this percentage was below 25 percent.

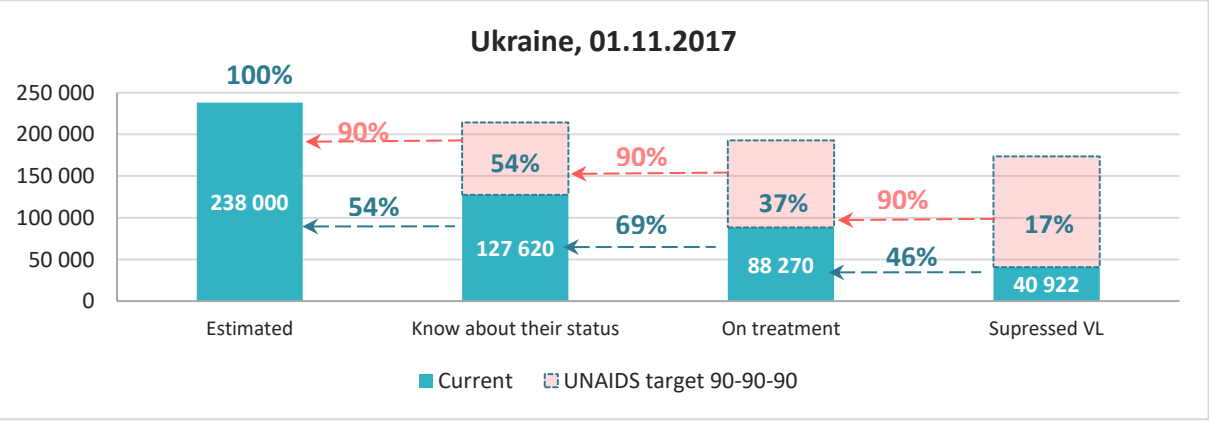


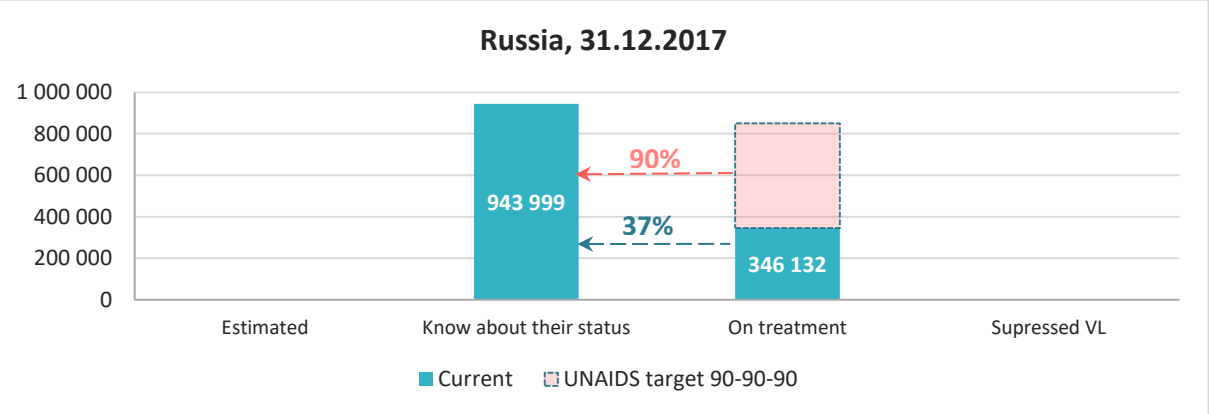












**Note: The indicators for cascades were calculated on the basis of information provided in national calculations. In Russia, at the time of preparing the national report, official data on the estimated number of people with HIV infection and the suppressed viral load was not available.*

The problem of the low effectiveness of the therapy can be solved by a set of measures, including:

- Revision of the used ARV therapy regimens due to inefficiency because of initial or acquired resistance.
- More intensive monitoring of therapy, including side effects management.
- Measures to increase adherence to therapy:
  - Low threshold programs for key groups
  - Consultation and information

In Kyrgyzstan, in 2018, a detailed plan was developed to increase adherence to ARV therapy in the country based on the results of a study conducted by Partner Network Association as a separate project. Such a plan is necessary for each of the countries of the region, since, judging by the indicators of suppressed viral load, the problem of adherence is relevant.

Measures to increase the coverage of therapy include a set of actions aimed at reducing the prices of the options used and the introduction of new, more economical and equally effective and safer drugs. Price-cutting can be achieved both through price negotiations with rights holders, and by eliminating barriers for competition from generic drugs. The prices can also be reduced through optimization of procurement processes, for example, by attracting international procurement agencies. Together with the reduction in prices, it is necessary to allocate additional resources for the procurement of drugs from the state. Each country has its own specific situation, and each national report has a plan for improving access at the country level.

Drug Registration

One of the important conditions for ensuring access to the drug in the country is the registration of the drug in the territory of this country. The issuance of a *market authorization* (MA) essentially means that the authorized national authority (as a rule, the Ministry of Health) permits commercial circulation of this drug on the market, and from the moment the MA is received it can be sold in pharmacies, procured for state needs, and so on.

The authors of the national reports in the framework of the research conducted a basic analysis of the laws governing the registration procedure and establishing the rules for selling drugs in the country, depending on the presence or absence of MA. Among other things, the national reports contain information on the conditions under which it is possible to deliver the drug to the market without registration.

Another key point in the legislation, to which the authors of the reports paid attention, is the possibility to register a drug via a *simplified procedure*. As a rule, a prerequisite to apply the simplified procedure is the availability of registration in one of the countries with so-called *strict regulatory agencies*. These traditionally include the agencies in the United States, the EU, Japan, Australia, Canada and Switzerland. It is believed that the standards of strict regulatory agencies are high enough so that it is possible to make a decision on the registration of a drug, based on the conclusion of one of these agencies.

The table below summarizes the analysis of laws related to the registration procedure in the seven countries. More information is provided in the national reports (see Introduction).

Table 1. Drug registration procedures in EECA countries

	Simplified registration availability	Procurement of unregistered drugs at the expense of the national budget	Comment on the possibility to procure unregistered drugs
Armenia	30 days' period, with existing registration in the USA, EU or Japan.	With GMP certificate of the manufacturer's country and a WHO's prequalification certificate; and/or with existing registration in the EU, USA or Japan.	Government Decision #1671-N 12/14/2017 on amending and supplementing Government Decision #502-N 02.05.2013.
Belarus	Not spelled out (requires clarification). Average registration period is 6-7 months. In some cases, it may be decided to conduct clinical trials, which make the registration procedure longer.	Yes, with WHO's prequalification or registration in ICH countries.	Quote from the technical specifications for the procurement of ART for 2018 (see National report, p. 23).
Kazakhstan	Not spelled out (according to the analysis, clarification is required). Under the existing laws, the examination at registration can take no more than 210 calendar days.	If the drugs are intended for the prevention and treatment of socially significant diseases (HIV infection among them).	According to open sources, this provision has not yet been practiced.
Kyrgyzstan	With WHO's prequalification or registration in one of these countries: EU, USA, UK, Switzerland or Japan.	Yes, according to the special list, including for socially significant diseases (HIV infection among them).	See page 13 of National report.

	Simplified registration availability	Procurement of unregistered drugs at the expense of the national budget	Comment on the possibility to procure unregistered drugs
Moldova	60 business days at the most in case of existing registration in one of these countries: EU, USA, Canada, Switzerland, Japan or Australia.	In special cases, provided that they are approved in the country of origin.	
Russia	Fast-track registration is possible (no more than 80 working days) in special cases, for example, drugs for orphan diseases (HIV infection does not apply) and the first three generic drugs (Federal Law-61).	In special cases, including for the needs of specific patients.	
Ukraine	With WHO's prequalification or registration in one of these countries: USA, EU, UK, Switzerland, Japan or Australia.	When procurement through international agencies, fast-track registration of drugs is carried out (up to 14 working days).	

At least in Armenia, Kyrgyzstan, Moldova and Ukraine, legislation in the area of registration is currently favorable for fast introduction of drugs to the market. It is noteworthy that, in particular, in Armenia and Kyrgyzstan, innovations regarding the fast-track registration procedures were actually adopted at the time of preparing of the national reports.

Traditionally, the legislation in the field of registration of drugs in the Russian Federation is one of the most rigid in the EECA region. The Russian Federation is actually the only one of the seven countries included in the study that requires clinical trials in the country in order to register a drug (in Belarus, the law provides for this possibility, but this is not mandatory in all cases). Perhaps the legislation of the Russian Federation in this area will change, partially thanks to the processes in the Eurasian Economic Union (EAEU), as well as the legislation of other member countries of the EAEU. From open sources[1] it is known about the existence of such initiatives, sponsored by both public organizations and executive authorities (for example, the Federal Antimonopoly Service of the Russian Federation).

In all countries, in one form or another, mechanisms allowing the procurement and import of unregistered drugs are provided. They are used, in particular, in the procurement of drugs for the treatment of socially significant diseases, drugs, prequalified by WHO, in special emergency cases of procurement, specific patients, etc. However, the simplicity of the mechanisms and ease of use are likely to vary from country to country. In any case, it is important that the countries' legislation provides workarounds when pharmaceutical companies refuse to go through the registration procedure for one reason or another, although the practical applicability and sustainability of this method will, again, be different depending on the national context.

In one particular case, in 2017, Armenia took steps to simplify the process of participation in open tenders of international agencies. Thus, in accordance with the decision of

[1] https://fas.gov.ru/publications/3297

the Government, drugs that are not registered in Armenia may be included in the procurement plan envisaged for the needs of the Ministry of Health. They must have a proper production certificate issued by the relevant competent authority of the country of origin and the prequalification of the World Health Organization, and/or be registered in any of the member countries of the European Union or in the United States of America or Japan.

National reports also contain tables with detailed lists of registered drugs. It follows from them that in all seven countries almost all basic options for treating HIV infection are registered. However, there are important exceptions and reservations that we consider necessary to be focused on. For example, in Kazakhstan at the beginning of 2018, the protease inhibitor atazanavir was not registered, while it was included in the national treatment guidelines, and Kazakhstan was included in the territory of the license agreement for atazanavir between BMS and the Patent Pool of Medicines. In some cases, the drugs are registered, but not actually used in treatment programs due to other barriers. This will be discussed in the next section on recommendations and restrictive lists.

Treatment Guidelines and Drug Lists

Restrictive lists

The decision on which drugs to use in treatment programs is made on the basis of various documents. In a number of countries, rigid restrictive lists with complex (and not always transparent formation mechanisms) are used. If the drug is not included in them, then it, in particular, is not allowed to be procured at the expense of the national budget. An example of such a list may be the List of Life-Saving and Essential Medicinal Products. In one form or another and under one name or another, it is used in all seven countries covered by the study.

Table 2. Restrictive lists in seven countries of EECA

	Usage of a list of essential medicinal products or analogue	Notes
Armenia	The list of essential drugs of the Republic of Armenia (LED)	Approved since 1994. In accordance with the Law on Medicines, the state must be provided with drugs from the LED.
Belarus	List of Essential Medicinal Products (LEMP) and Republican Formulary of Drug Products	The list of main drugs includes medicines for preferential (also including free) provision. Under the Law on Medicinal Products, the state ensures the availability of medicines, primarily included in the LEMP.
Kazakhstan	Kazakhstan National Formulary of Drug Products	The list of drugs with proven clinical efficacy and safety, containing information about drugs and prices, which is the basis for the development of drug products formularies of health organizations and the formation of lists for the procurement of drug products.
Kyrgyzstan	List of Life-Saving and Essential Medicinal Products (LLEMP)	Based on the LLEMP, the nomenclature for the procurement of drug products is formed.
Moldova	List of Vital and Essential Drugs (LVED)	Based on the list, the procurement of drug products is carried out at the expense of public sources.
Russia	List of Vital and Essential Drugs (LVED)	Used primarily to set the maximum sale prices for drugs. Priority is given to the procurement of drugs within health programs, including federal budget.
Ukraine	National List of Essential Medicines (National List)	Drugs that are not included in the National List cannot be procured at the expense of public funds (there are exceptions). The National List will not apply to international organizations' procurement.

The impact of the list of essential medicinal products on the creation of the list of drugs for procurement varies from country to country. Thus, in the Russian Federation, the inclusion of a medicinal product in the LVED makes it possible to procure it from federal budget resources. In this case, the maximum selling price of the drug is recorded, which (including VAT and regional allowances) is prohibited to exceed during the bidding process. The results of observations of the ARV drug market in Russia show that the price of the drug significantly (in some cases by many times) decreases after inclusion in the LVED.

In addition to the lists of essential medicinal products, additional restrictive lists are used in some countries. In Kazakhstan, for example, to ensure full access to the drug, it is necessary to include it in at least three lists:

- Kazakhstan National Formulary of Drug Products
- List of drugs as part of free medical care and compulsory health insurance system

- List of drugs for procurement by a single distributor (SD)


MED НОВОСТИ

Минздрав попросили включить "Тенофовир" в список жизненно необходимых лекарств

Распечатать

Изображение из блога организации "Пациентский контроль"

19 июня 2013 года, 11:08

КОММЕНТИРОВАТЬ

ЧИТАТЬ ЕЩЕ: ЖНВЛП, ЛЕКАРСТВА ОТ ВИЧ, ОБНОВЛЕНИЕ СПИСКА, ПАЦИЕНТСКИЕ ОРГАНИЗАЦИИ, ТЕНОФОВИР

24 пациентские организации России попросили главу Минздрава Веронику Скворцову включить «Тенофовир» и ряд других лекарств, применяемых при лечении ВИЧ-инфекции, в список жизненно необходимых и важнейших лекарственных препаратов (ЖНВЛП). Об этом сообщается в пресс-релизе, поступившем в редакцию МедНовостей.

The relevant sections of the national reports contain the names of the lists, the number of orders, information on the meaning of this list for the procurement of medicines, as well as the lists of ARV drugs included in these lists. Also described are the examples of how the absence of a drug in the list adversely affects the access even if there is registration (see the previous section). In this regard, an example with several drugs in the Russian Federation, in particular, with emtricitabine and rilpivirine, is indicative. The drugs were registered in the territory of the country several years ago, but until 2018 they were not procured by the Ministry of Health, primarily because they had not been included in LVED. Procurement by regional customers are extremely limited in volume. More information about this situation can be found in the report on the Russian Federation. In the period from 2011 to 2015 Patient organizations in the Russian Federation spent a lot of efforts to achieve the inclusion in the LVED and the bylaw for the procurement of ARV drugs from the federal budget resources[2] to procure tenofovir (one of the basic options for treating HIV infection in the world). After being added to the list, its price decreased by many times, and now tenofovir and lamivudine are the most popular combination of NRTI in Russia.

In Kazakhstan, the absence of a drug in at least one of the above-mentioned lists leads to the fact that the drug is not procured for public funds and is not available to patients. The presence of the drug in the correspondent lists is also relevant for Kyrgyzstan; therefore, patient organizations periodically draw public attention to the importance of the formation of LLEMP. In Ukraine, as it can be seen in the table above, the situation is more favorable: there are exceptions in which even in the absence of a drug in the so-called National List, access to the drug can still be ensured.

In general, in at least three countries (Russia, Kazakhstan and Kyrgyzstan), judging by the texts of the national reports, public organizations seek to influence the development of lists to improve the access to drugs. Below are the main factors to work on:

- ensuring *transparency* and *regular* updates of the lists,
- admission of *public organizations* to this process, and
- elimination of *redundant lists* that further restrict access to drugs.

Thus, the Russian Federation abolished a bylaw on the procurement of ARV drugs and drugs for the treatment of viral hepatitis B and C from the federal budget resources (the so-called Bylaw 1438 and 1480). It also contained a list of drugs to be procured, and in the case of tenofovir, public organizations had to make additional efforts to have the drug included in this bylaw.

National recommendations

National HIV treatment guidelines may also influence the choice of drugs for treatment programs. Below is a brief overview of these documents, which indicates that all seven countries generally follow the 2016 WHO recommendations.

[2] Currently expired.

In all countries, the *test and treat* approach is reflected in one form or another in national protocols. According to this approach, it is recommended to consider the possibility of prescribing ARV therapy immediately after HIV infection has been diagnosed.

The overview of treatment regimens is presented in the table below.

Table 3. Overview of first-line treatment regimens in the seven EECA countries

Country	Preferred first-line regimen, 2017	The actual first-line regimen	The preferred first-line regimen in the new protocols for 2018
Armenia	TDF+3TC (or FTC)+EFV TDF+3TC (or FTC)+DTG	TDF/FTC/EFV **(FDC)**	The same
Belarus	TDF+3TC (or FTC)+EFV	TDF/FTC **(FDC)**+EFV AZT/3TC **(FDC)**+EFV	The same
Kazakhstan	TDF+3TC (or FTC)+EFV	TDF/FTC/EFV **(FDC)** TDF/FTC **(FDC)**+EFV	The same
Kyrgyzstan	TDF+3TC (or FTC)+EFV	TDF/FTC/EFV **(FDC)**	The same+DTG is planned
Moldova	TDF+3TC (or FTC)+EFV	TDF/FTC/EFV **(FDC)** TDF/3TC /EFV **(FDC)**	TDF+3TC (or FTC)+DTG
Russia	TDF+3TC (or FTC)+EFV	TDF+3TC+EFV (in the form of individual drugs)	TDF+3TC (or FTC)+EFV
Ukraine	TDF+3TC (or FTC)+EFV	TDF/3TC/EFV **(FDC)**	DTG is planned

Table 4. Overview of second-line treatment regimens in the seven EECA countries

Country	Preferred second-line regimen, 2017	The actual second-line regimen	The preferred second-line regimen in the new protocols for 2018
Armenia	TDF+FTC (or 3TC)+ATV/r or LPV/r AZT+FTC (or 3TC)+ATV/r or LPV/r	TDF/FTC **(FDC)**+LPV/r	
Belarus	AZT+3TC+LPV/r (or ATV/r[1]) TDF+FTC (or 3TC)+LPV/r (or ATV/r)	TDF/FTC **(FDC)**+LPV/r AZT/3TC **(FDC)**+LPV/r	AZT+3TC+LPV/r (or ATV/r[1]) TDF+FTC (or 3TC)+LPV/r (or ATV/r)
Kazakhstan	AZT+3TC+ATV/r TDF+3TC (or FTC)+LPV/r	AZT/3TC **(FDC)**+LPV/r TDF/FTC **(FDC)**+LPV/r AZT+3TC+ABC **(partially FDC)**	
Kyrgyzstan	2 NRTI+LPV/r	AZT/3TC **(FDC)**+LPV/r TDF/FTC **(FDC)**+LPV/r	2 NRTI+ATV/r or LPV/r
Moldova	AZT+3TC (or FTC)+LPV/r	AZT/3TC **(FDC)**+LPV/r TDF/FTC **(FDC)**+LPV/r	AZT+3TC (or FTC)+ATV/r (or DRV/r)
Russia	2 NRTI+ATV/r, DRV/r, LPV/r	2 NRTI+LPV/r 2 NRTI+ATV (or ATV+r) 2 NRTI+DRV+r (only AZT/3TC as **FDC**)	2 NRTI+DTG, ATV/r, LPV/r, DRV/r
Ukraine	TDF+FTC (or 3TC)+LPV/r	TDF/FTC **(FDC)**+LPV/r	

Some explanation should be given to these two tables. “Actual regimens” refer to those regimens that were used in clinical practice, according to data provided by national departments, as well as the analysis of the procurement structure of drugs. In some countries, the information on how to change treatment approaches in 2018 was available, and we considered it important to include it in this version of the report. Also in the national reports, comments were made on how real it is to implement treatment recommendations in practice.

Thus, the report on Belarus points out that “there are objective obstacles to following the 2017 recommendations of WHO on switching to new drugs: the inclusion of DTG-based regimens in alternative first-line regimens is limited by the availability of patent protection and the associated high price of the drug ($2,290 for the annual course in 2017). EFV400 and RAL drugs are currently not registered in Belarus, there are no ATV/r and DRV/r drugs in the form of a fixed combination (due to the presence of patent protection on RTV). In 2018, the procurement of atazanavir is not planned, although the drug is included in the preferred second-line regimens. In 2017, 40 courses of atazanavir were procured.

In Kazakhstan, as it was noted in the previous section, atazanavir is included in the preferred second-line regimen, but despite this, the drug has not yet been registered in the Republic of Kazakhstan and is not used in treatment programs there.

In Kyrgyzstan, the new revision of the protocol includes new drugs: atazanavir (ATV), darunavir (DRV), dolutegravir (DTG) and rilpivirine (RPV). Dolutegravir is present in alternative regimens with “if available” reference.

Procurement Analysis

When conducting a procurement analysis, public organizations traditionally seek to receive answers to three main clusters of questions:

1. How many drugs are being procured? How many patients is this volume intended for?
2. Which drugs are being procured? Is the choice of drugs consistent with international and national guidelines?
3. At what prices are the drugs being procured? How much money is spent eventually? Is there potential to save money?

Number of patients

In each national report, the data on the number of patients (obtained as a result of the procurement structure analysis) was compared with official data on the number of people receiving ARV therapy.

In some cases, these data practically coincided, in some cases discrepancies were revealed, the reasons for which were established in each case separately. Possible explanations for discrepancies (assuming the calculations were correct) were: the provision of incomplete data, the availability of drugs (the so-called "carry-overs"), the procurement of a larger number of drugs to provide a "buffer stock".

The following methodology was used to calculate the potential number of patients: All drugs were divided into two groups in accordance with the basic rules for the selection of antiretroviral therapy: drugs of the nucleoside (nucleotide) reverse transcriptase inhibitors (NRTIs) group were placed in the same group, the other drugs that are summarized under the name of "base drugs" in this report were put in the second group.

The following formula was used to calculate the number of patients receiving base or combination drugs containing the whole regimen: **the total amount of tablets/amount of tablets per day/365**. The NRTI drugs were calculated separately. The calculations took into account that the classical regimen of ARV therapy contains two NRTI drugs. The total number of patients was calculated on the basis of the estimated number of patients receiving the "base drugs" and the entire-regimen-in-one-tablet combination drugs. The resulting value was compared with the number of patients receiving NRTI. These two groups are not cumulative, since the classical regimens of ARV therapy include two drugs of the NRTI group (one of them, as a rule, lamivudine or emtricitabine) and the base preparation (most often from the class of non-nucleoside reverse transcriptase inhibitors (non-NRTI), protease inhibitors (PI) or integrase inhibitors (II)).

This methodology has limitations. Firstly, as noted above, with a one-time analysis, the methodology does not take into account the presence of possible existing stocks of drugs ("carry-overs"). Secondly, it does not take into account rare combinations of drugs (for example, combinations in the same regimen of non-NRTI and II classes) and the fact that in clinical practice drugs may not be administered in accordance with the recommendations. However, the figures obtained provide a general overview of the number of patients and the structure of ARV regimens, and can be used in a dialogue with authorities responsible for planning and procuring drugs.

Table 5. Data on the number of patients in seven countries of EECA

	Official data	Percentage of people aware of the diagnosis	Percentage of the estimated amount	Procurement Analysis Data	Comment
Armenia	1,530	68%	45%	1,586	According to government and international procurement in 2017, the estimated number does not include pediatric forms.
Belarus	9,990	54%	39%	12,435	By the end of 2017, it was expected to reach 10,880 people with treatment. The procured volumes cover the planned demand, leaving an extra supply of almost 2,000 courses of drugs. The estimated number does not include pediatric forms. Data as of September 30, 2017. In the 3rd quarter of 2017, there was an active involvement of PLHIV in therapy, taking into account the transition to universal access from 2018. The buffer stock for individual drugs is from 3 to 5 months.
Kazakhstan	11,482	55%	44%	10,626	Patients who received ARV therapy in 2017 were allegedly provided from carry-over stock of 2016 procurement and 2017 AVR procurement drugs. The estimated number does not include pediatric forms.
Kyrgyzstan	3,024	53%	36%	4,033	The estimated number roughly corresponds to the number of patients on ARV therapy by the end of 2017, with a margin of 1,000 courses. The estimated number does not include pediatric forms.
Moldova	4,491	57%	29%	3,560	The values are the estimated number of courses procured from various sources in 2016. Patients receiving therapy in 2016 were supposedly provided from carry-over stocks of 2015 and 2016 procurements. It is also possible that incomplete procurement data was provided in 2016. The estimated number does not include pediatric forms.
Russia	346,132	37%	no data*	360,000	The estimated number does not include pediatric forms. *Data on the estimated number are not available.
Ukraine	88,270	69%	37%	77,051 (no including pediatric forms), 77,574 (including pediatric forms)	Patients receiving ARV therapy in 2017 were allegedly provided from carry-over stock of 2016 procurement and procurement at the expense of international resources (Global Fund, PEPFAR).

According to the analysis, the following fact is obvious: **all countries should significantly increase the scope of therapy simultaneously optimizing the choice of drugs in accordance with changes in international standards of treatment.** The remarks on drug selection are given in the section to follow.

Drug selection

The table below summarizes the procurement and use of several key base drugs.

Table 6. Share of base drugs in seven countries of EECA from the number of patients receiving therapy, 2017[3]

	EFV	LPV/r	NVP	DTG	RPV	DRV	ATV	RAL	ETV	3NRTI+/- 3rd drug
Armenia*	72%	23%	4,1%	0,6%	-	0,06%	0,75%	0,48%	-	-
Belarus	68%	19%	11%	0,5%	-	0,4%	0,5%	-	-	1,2%
Kazakhstan	49%	19%	11,6%	-	-	0,05%	-	-	0,06%	10,95%
Kyrgyzstan	83%	9%	6,1%	-	-	-	-	-	-	1,2%
Moldova**	80%	13%	6,4%	-	-	0,45%	0,32%	-	-	0,39%
Russia*	45%	27%	6%	0,1%	0,06%	4,16%	10,12%	2,31%	3,44%	-
Ukraine*	61%	23%	2,3%	12,4%	-	0,31%	-	0,41%	0,03%	-

**For the Russian Federation, Armenia and Ukraine, the share is calculated from the estimated number of patients according to the procurement analysis. In Ukraine, only adult forms were considered. For other countries, the proportion of the official number of patients on regimens is considered.*
Note: 3NRTI regimens used in Kazakhstan: AZT/3TC/ABC, (AZT/3TC+ABC), (AZT+3TC+ABC), AZT/3TC+TDF (AZT+3TC+TDF), TDF/FTC+ABC, TDF/FTC+AZT.
3NRTI regimens used in Belarus: (AZT+3TC)+ABC (92% of all 3NRTI regimens),), in Kyrgyzstan (AZT+3TC)+ABC (63% of 3NRTI), AZT/3TC+TDF (28% of 3NRTI)
***Moldova: 3NRTI+3rd drug, the drug does not add up to the others, because there is an intersection with the 3rd drug.*

Table 7. Number of patients receiving certain base drugs in seven countries of EECA, 2017[3]

	EFV	LPV/r	NVP	DTG	RPV	DRV	ATV	RAL	ETV	3NRTI+/- 3rd drug
Armenia*	1,141	357	65	10	-	1	12	1	-	-
Belarus	6,774	1,860	1,098	50	-	42	52	-	-	114
Kazakhstan	5,614	2,226	1,335	-	-	6	-	-	7	1,257
Kyrgyzstan	2,523	283	183	-	-	-	-	-	-	35
Moldova	3,502	586	282	-	-	20	14	-	-	17 (14 per 3NRTI+3rd drug)
Russia*	161,352	96,117	21,392	350	229	14,828	36,083	8,272	12,261	-
Ukraine*	47,161	18,010	1,741	9,553	-	242	-	320	26	-

An analysis of the procurement structure of ARV drugs shows several trends. Treatment regimens in seven countries in the region were mainly based on two “base drugs”: efavirenz 600 mg (EFV) and lopinavir/ritonavir 200/50 mg (LPV/r). Efavirenz, in the dosage of 400 mg, is practically not used. Dolutegravir, which is recommended as an alternative first-line drug in the latest version of WHO protocols, in 2017 was relatively widely used only in Ukraine.

[3] Except in Moldova (where data of 2016 was only available), and Belarus (data as of September 30, 2017).

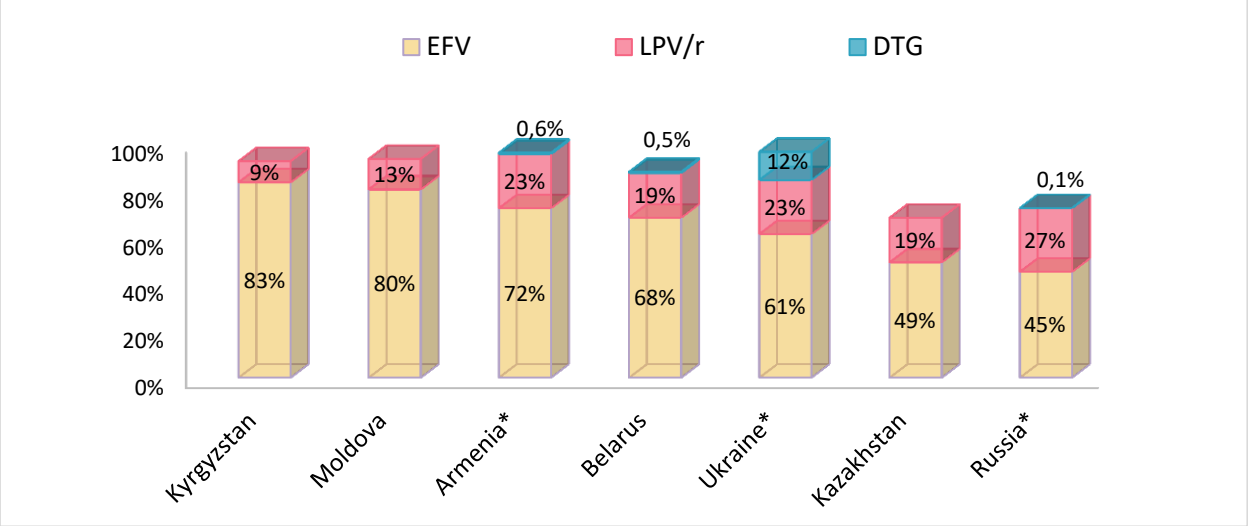
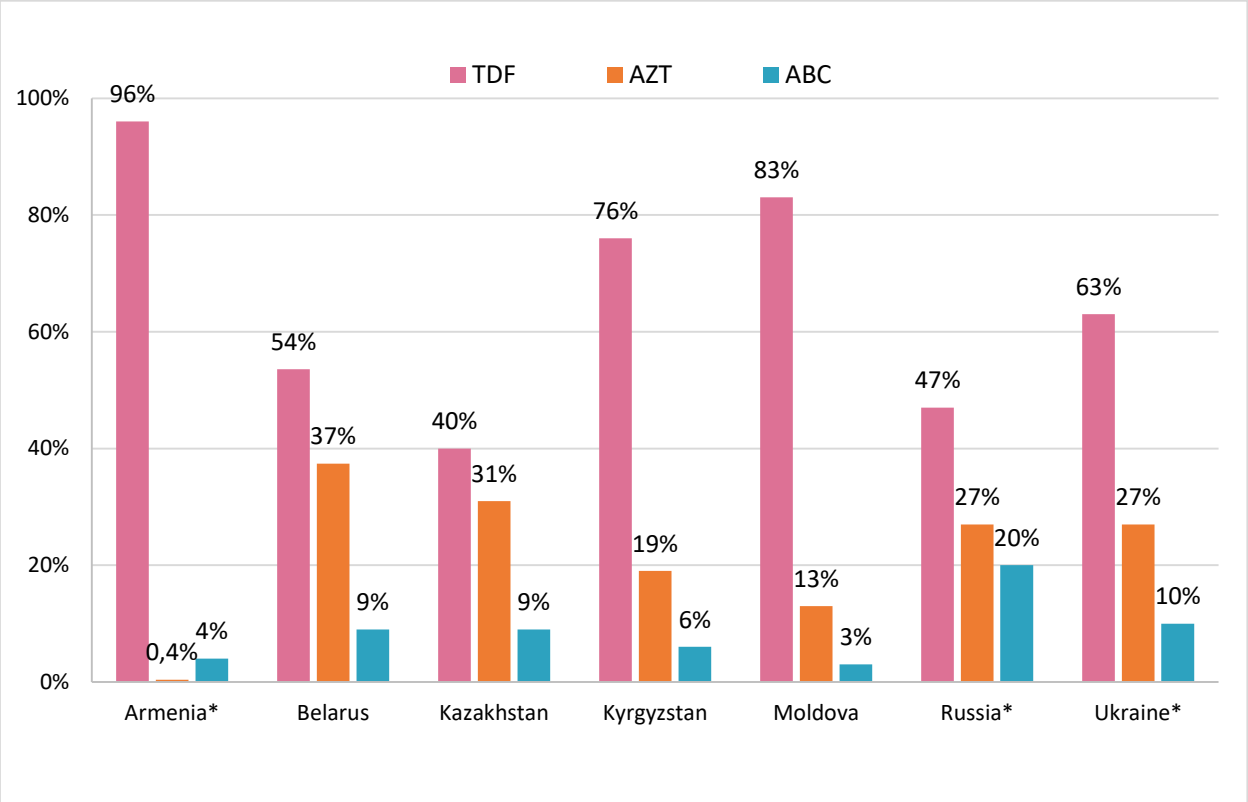


Figure 1. Shares of efavirenz, lopinavir/ritonavir and dolutegravir in seven EECA countries

Among the drugs of the NRTI group, mainly tenofovir/emtricitabine (TDF/FTC) or tenofovir and lamivudine (TDF+3TC) prevailed. Abacavir/lamivudine (ABC/3TC) is used less frequently, and zidovudine/lamivudine (AZT/3TC) is still used to varying extents.



**In the Russian Federation, Armenia and Ukraine, the share is calculated from the estimated number of patients according to the procurement analysis. For other countries, the proportion of the official number of patients on regimens is calculated.*
Note: the drug share includes the combination forms in which this drug is included (for example, lamivudine/zidovudine is referred to zidovudine, abacavir/lamivudine is referred to abacavir, etc.). 3 NRTIs regimens were excluded from the calculation.

Figure 2. Shares of drugs from the NRTI group in the procurement structure (excluding lamivudine and emtricitabine)

It is important to pay attention to the fact that in Kazakhstan, in particular, a significant percentage of patients (almost 11%) receive regimens consisting of 3 NRTIs in different combinations (see Table 6 above). At the same time, another 10% receive the so-called "other regimens" (this is reflected in the national report). This is largely due to the inaccessibility of drugs of the 2nd and 3rd lines (except LPV/r). As it can be seen from the table, the percentage of people on other protease inhibitors and integrase inhibitors is less than 1%. It should be kept in mind that the effectiveness of therapy in Kazakhstan is 55% of the number of people receiving therapy, this is one of the lowest in the EECA region (46% in Ukraine).

In all countries, *except Russia*, *combination forms* are widely used. The figures below show the approximate percentage of patients receiving the regimen in one tablet (the so-called "3 drugs in one tablet", "3 in 1" or DFC) and patients receiving monocomponents (single pills). It is important to note that the combination base of NRTIs is widely used in Belarus, and in 2018 it is planned to increase DFC regimens, according to closed contracts. The percentage of patients receiving the regimen in the form of individual drugs is just over 11%. There is a clear tendency to use combination products in the countries where procurement at the expense of the Global Fund predominate (Moldova, Kyrgyzstan and Armenia).

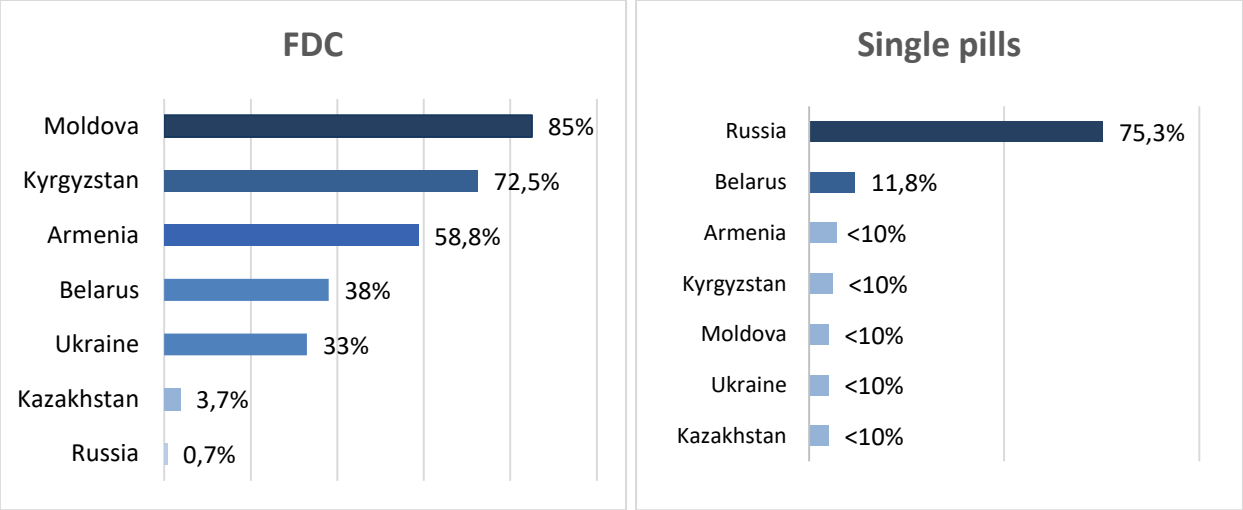


Figure 3. Combination drugs (3 in 1) and monocomponents (single pills) in EECA countries

It should be kept in mind that at least four countries (Belarus, Kyrgyzstan, Kazakhstan and Moldova) use regimens consisting of 3 NRTIs or 3 NRTI plus "base drug".

The second-line regimen is dominated by the drug lopinavir/ritonavir. Atazanavir and darunavir are practically not used in the countries of the EECA region, with the exception of the Russian Federation, where atazanavir and darunavir are represented by several generics and are procured in fairly large volumes. Darunavir or (to be more exact) its solvate form[4], in most countries is protected by a patent, and, apparently, the main obstacle to expanding access to it is the price (see the section below). Generics of darunavir are registered in the Russian Federation, representing an amorphous form, which, according to manufacturers, do not violate the patent. Atazanavir, despite the possibility of supplying generics under an agreement between BMS and the Patent Pool of Medicines, is largely ignored by the clinical community in the countries of the region. One of the key barriers to access to atazanavir (in particular, the generics of atazanavir/ritonavir) and darunavir is the patent for a thermostable form of ritonavir with which these drugs should be combined.

[4] The information on patents for the corresponding forms of darunavir can be found, for example, on the Patent Pool website of medicines.
http://www.medspal.org/?keywords=darunavir&country_name=Russian%20Federation

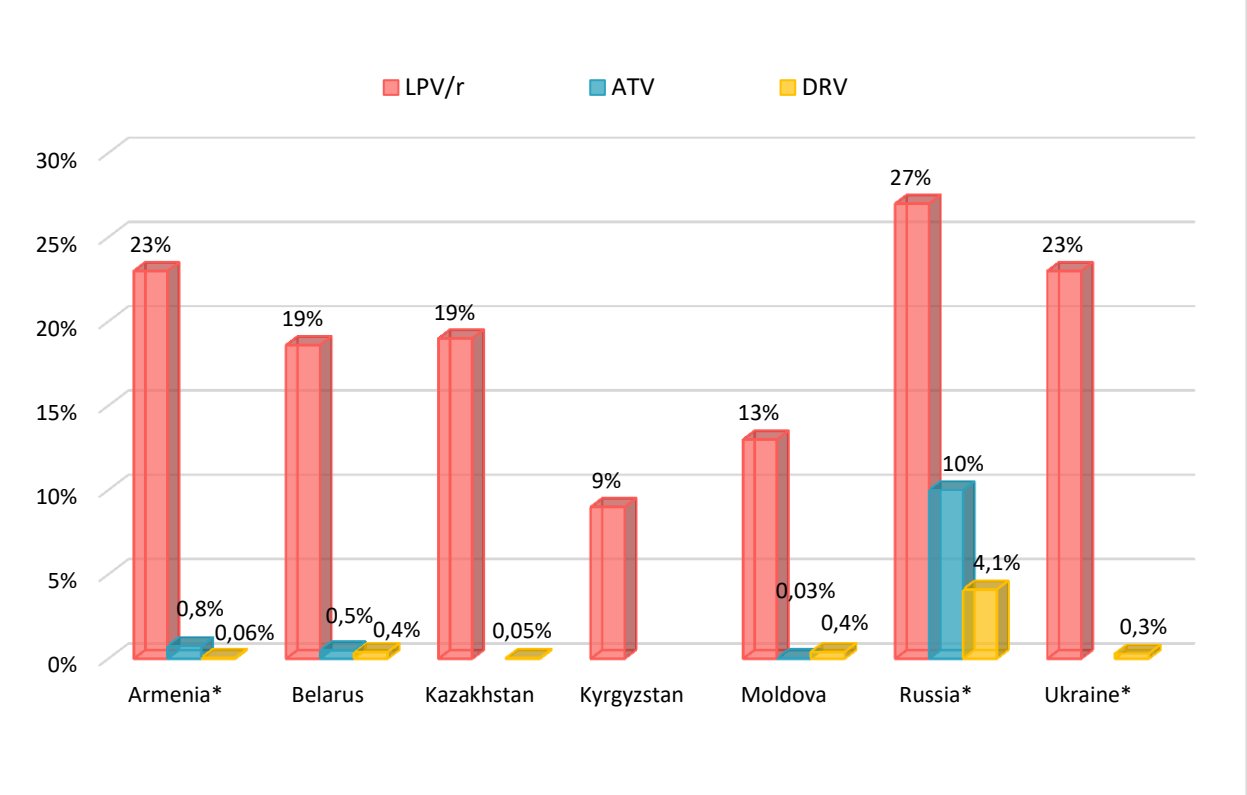


Figure 4. Shares of protease inhibitors in the overall procurement structure

In the countries covered by the study, except for the Russian Federation and Kazakhstan, the second generation non-NRTI drugs (etravirine, rilpivirine, elsulfaverin) are practically not used. In Kazakhstan, etravirine is used to a limited extent. All of these drugs are patent-protected. Rilpivirine is included in the latest version of treatment protocols in Kyrgyzstan, but the prospects for using the drug due to patent protection remain dim. The Janssen initiative to sell rilpivirine at a special price ($5 per package) has not been implemented.

Inhibitors of integrase in 2017 were practically not used in the region, except for Ukraine and Russia. The main II in the Russian Federation in 2017 was raltegravir. In 2018, a significant increase in the use of dolutegravir in the region as a whole is expected. Thus, in Russia, according to the procurement schedule for 2018, it is planned to procure about 13.5 thousand annual courses of dolutegravir.

Drug prices

The tables below present the prices of main drugs in 2017[5], broken down by class.

Table 8. Prices for drugs of NRTI group in seven countries of EECA, price per month, $.

Country	Procurer	AZT/3TC	ABC/3TC	TDF/FTC	TDF	3TC 150 mg	ABC 300 mg
Armenia	GF	5.1 (in 2018)	12.6	5.25	-	2.11	10.2
Belarus	MoH	23.02 (generic)	-	74.81 (generic)	61.65 (generic)	34.46 (generic)	35.21 (generic)
	GF	-	-	-	-	-	-
Kazakhstan	UNICEF	-	-	51.6 (original)	3.5	-	-
	MoH	39.6 (original)	115.68 (original)	-	-	77 (generic)	94.46 (original)
		143.2 (generic)	51.52 (generic)	-	-	28.72 (original)	-
Kyrgyzstan	GF	4.94-5.9	11.9-12.75	4.95	2.72-3.2	-	9.5- 9.9
Moldova	MoH	11.4	168 (original)	-	-	-	-
	GF	7.4	16.95	6.7	5.88	-	-
Moldova	MoH	12.81	74.11* (original)	197.75 (original)	5.99	1.96	15
Ukraine	UNICEF	5.67	12.13 (generic)	4.9	2.8	2.09	10.7 (generic)
	NAMS	12.48	-	8.5	6.93	-	-
	GF	6.25	29.07 (original)	5.36	3.19	2.02	24.22 (original)
	PEPFAR	5.95	11.2 (generic)	4.61	3.2	1.9	9.24 (generic)

** In Russia, the procurement of a combination of ABC/3TC was only within the regional budget*

According to the results of the analysis of prices for drugs of the NRTI group, several conclusions can be made.

Firstly, the extremely high prices of NRTIs in Belarus and Kazakhstan compared to other countries (3TC/AZT, ABC/3TC, TDF/FTC)[6] are striking. It is also worth noting the extremely high price of ABC/3TC in Moldova (168 US dollars per package, with the most common price in the region of 11-12 US dollars per package and the price of the original 115 US dollars in Kazakhstan).

In Kazakhstan, generic drugs of lamivudine and lamivudine/zidovudine are about three times more expensive than the original drug. This is due to the support policy of the domestic manufacturer. In Belarus, the high prices for the NRTI group of drugs (see paragraph above) are also related to the fact that the drugs are supplied by the domestic manufacturer, who carries out the pre-packaging and packaging of the finished dosage form. Obviously, in this case, the policy of supporting local pharmaceutical companies leads to an evident overpricing and, as a consequence, restricted access. At the same time, it is worth noting that the entry into the market of the second large national manufacturer in 2018 led to the

[5] Except for Moldova, where only data for 2016 were available.

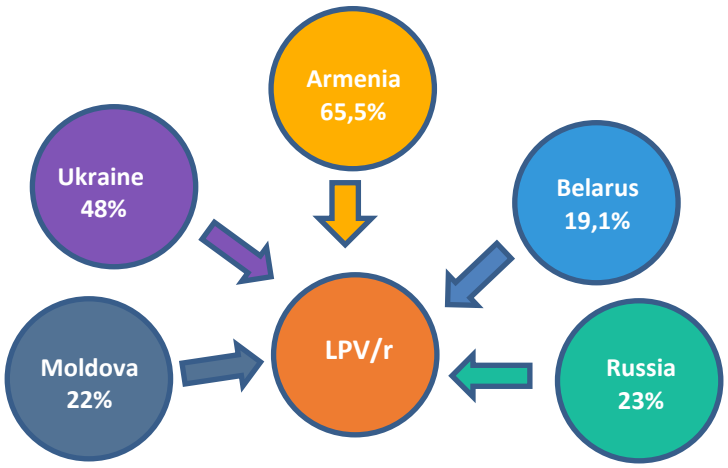
[6] It is noteworthy that for procurements in 2018, the price per TDF/FTC package decreased from 74.81 to 11.32 USD, while the price per AZT/3TC package decreased from 23.02 to 7.31 USD.

fact that the average cost of the annual ART regimen decreased 3.1 times (according to preliminary data), which indicates a favorable influence of the competitive environment.

In the Russian Federation, the NRTI base is relatively cheap, with the exception of the combination drugs ABC/3TC and TDF/FTC. However, it is important to note that in the Russian Federation these combination forms are practically not used, as mentioned above.

Table 9. Prices for protease inhibitors in seven countries of EECA, price per month package, $

Country	Procurement type	LPV/r 200+50 mg	ATV 300 mg	DRV 600 mg
Armenia	GF	60.8	16.5 (ATV/r)	72.5 (original)
	MoH	64	-	-
Belarus	GF	60.8	17 (generic)	-
	MoH	-	-	267.44 (generic)
Kazakhstan	UNICEF	61.2	-	379.77 (original)
Kyrgyzstan	GF	16.92 (generic) ($60.8 in 2017 and 2018)[7]	-	-
Moldova	GF	60.8	20.95	109.2 (generic)
Russia	MoH	79.23	83.61 (generic/original)	370.62 (generic/original)
Ukraine	UNICEF	64.78	-	483.39 (original)
	NAMS	68.85	-	503.99
	GF	60.8	-	-
	PEPFAR	60.8	-	453.66



LPV/r budget shares, 2017 data

In the class of protease inhibitors, lopinavir/ritonavir is the most popular drug. The drug is under patent protection, and the price for it ranges from 60 to 80 US dollars per package, despite the fact that the generic drug, as can be seen from the procurement analysis in Kyrgyzstan, costs about $17 per package. Lopinavir/ritonavir in some countries is the most "cost-intensive" drug, as it consumes most of the funds from the consolidated budget for ARVT (see figure below). In a number of countries, primarily Ukraine, Russia and Kyrgyzstan, reducing the price of lopinavir/ritonavir or replacing it with alternative drugs (dolutegravir, atazanavir, darunavir) in order to reduce the burden on the budget and provide more people with ARV therapy is one of the priority areas of work indicated in the report.

[7] According to preliminary information from Partners Network Association, in 2016 generic was procured at a price of 16.92, stocks of which have been moved over to 2017. In 2017, original drug was procured for $60 with an extra stock for 2018. For 2018-2020, the estimated price is $60.

According to preliminary information, in Belarus in 2018 the share of LPV/r increased to approximately 35% (despite the fact that LPV/r in 2017 was part of 21% of the regimens, and in 2018 it will be only 12% of the regimens). Such an increase in the share of the cost of LPV/r is relative and occurs against the background of a decrease in the cost of other ARV drugs and a constant cost of the original version of LPV/r.

Atazanavir in the form of generic is a cheaper option (from $16.5 to $21 per pack). At the same time, atazanavir was supplied to a number of countries as a combination drug, atazanavir/ritonavir (for example, Armenia). For atazanavir, the access to ritonavir is a problem, because the heat-resistant form of ritonavir (heat-stable) is under patent protection, and the patent belongs to AbbVie. Accordingly, despite the fact that many countries in the region are included in the Patent Pool drug license for atazanavir and can procure generics, when procuring the atazanavir/ritonavir combination they face a situation where the patent owner can block the supply of the drug to the market. Solution options: wait for the atazanavir/cobicistat option to appear or somehow eliminate the patent barrier, for example, dispute the patent for ritonavir, work on issuing a compulsory license for ritonavir, or negotiate with the patent owner.

Darunavir is a more expensive option than lopinavir/ritonavir or atazanavir/ritonavir, and in the case of darunavir, there is also the problem of access to ritonavir. It should be noted that in some countries (for example, Russia) generic darunavir (amorphous form) is already available, and the price of the drug in 2018 decreased significantly. Darunavir, including its combination with ritonavir or cobicistat, is one of the priority options, access to which should be improved by reducing the price.

Table 10. Prices of non-NRTI products in seven countries of EECA, price per month package, $

Country	Procurer	EFV 600 mg	NVP 200 mg
Armenia	GF	3.07	2.2
Belarus	MoH	18.01 (generic)	12.19 (generic)
Kazakhstan	UNICEF	3.04	1.87
	MoH	45.6 (original)	25.38 (original)
Kyrgyzstan	GF	2.62–2.9	1.92
Moldova	MoH		4.8
	GF	4.32	3.78
Russia	MoH	11.49	6.43 (generic)
Ukraine	UNICEF	3.42	-
	NAMS	-	-
	GF	3.07	2.47
	PEPFAR	2.65	1.8

First generation drugs of non-NRTI group (efavirenz, nevirapine) cost many times less than the second generation non-NRTIs, which, as noted above, are practically not used in the EECA region (a relatively significant exception, perhaps, is the Russian Federation). Efavirenz is slightly more expensive than nevirapine, however, as noted above, it significantly exceeds nevirapine in terms of procurement, and this is consistent with international recommendations, in which efavirenz is the preferred option, and nevirapine is an alternative. The original efavirenz, procured for children in Kazakhstan, is expected to be several times more expensive than generic (see table).

Table 11. Prices for integrase inhibitors in seven EECA countries, price per package, $

Country	Procurer	DTG 50 mg	RAL 400 mg (original only)
Armenia	GF	3.67	350
Belarus	GF	190.8 (original)	-
Kazakhstan	-	-	-
Kyrgyzstan	-	-	-
Moldova	-	-	-
Russia	MoH	247.49* (original)	524.79
Ukraine	UNICEF	5.71	372.94
	NAMS	234.2 (original)	365.73
	PEPFAR	5	350

*In Russia the procurement of DTG 50 mg was only carried out at the expense of regional budget.

Comparing prices for integrase inhibitors demonstrates that dutegravir, especially its generic form, is a significantly cheaper option than raltegravir. Raltegravir is under a patent in most countries of the region, the patent holder has not issued a license for the production of generic form of the drug for adults (the license is only for the pediatric form), consequently, raltegravir generics are not available on the market.

Table 12. Prices for combination drug TDF/FTC/EFV in seven EECA countries, price per package per month, $

Country	Procurer	TDF/FTC/EFV
Armenia	GF	7.41
Belarus	MoH	108.23 (generic)[8]
Kazakhstan	UNICEF	7.5
Kyrgyzstan	GF	6.85- 7.99
Moldova	MoH	13.2
	GF	10.6
Russia	MoH	-
Ukraine	UNICEF	8.08 (generic)
	NAMS	-
	GF	30 (original)
	PEPFAR	6.54 (generic)

When analyzing the prices of tenofovir/emtricitabine/efavirenz drug, the extremely high price of the generic in Belarus draws attention if compared to prices in other countries. In 2018, the competition between two national suppliers reduced the price by almost three times (from 108.23 to 39.26 USD), but the cost still remains relatively high. Further reduction of the cost of this drug or its replacement with other, cheaper and modern options should be one of the priorities in the work.

The prices in the procurement of international donors and with the participation of international procurement agencies and organizations (for example, UNICEF) are significantly lower than in the procurement of ministries of health. For clarity, below are the comparisons of prices for efavirenz 600 mg and tenofovir 300 mg. Drugs without patent protection to eliminate the factor of barriers associated with intellectual property were selected.

[8] In 2018, according to preliminary data analysis, the price has decreased significantly and was 39.26 USD per month.

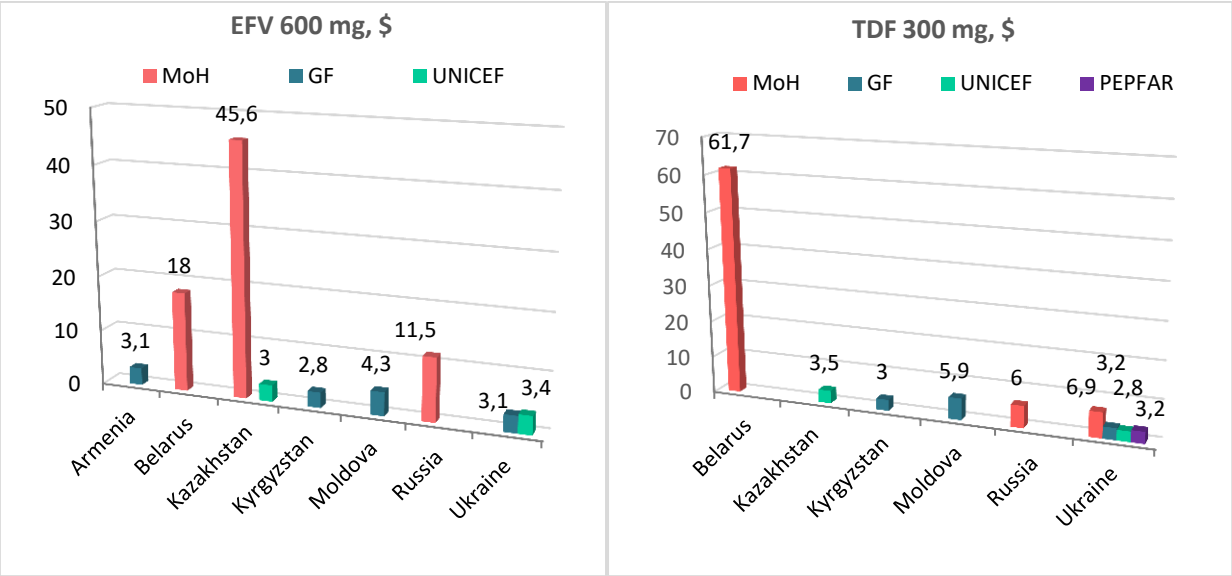


Figure 5. Comparison of prices for generic products with various procurement mechanisms

In general, price analysis shows several obvious trends:

- Prices for generic-free drugs (second generation, PI, II) limit access to these drugs, and they are used in extremely small amounts. The exception is lopinavir/ritonavir, which is used relatively widely, and at the same time it is a huge burden for the budget.
- Prices in public procurement are higher than prices in procurement with involvement of international agencies.
- The trend of supporting domestic companies during the bidding leads to a significant overpricing and restricting the access.

These trends point to possible areas of work that will be discussed in the next section.

Key Conclusions

This section contains the main observations from the results of the seven national reports, as well as possible ways which countries may take to fight the epidemic.

1 Conclusion 1. Relatively low treatment coverage and rates of suppressed VL

The analysis of collected data illustrating the treatment cascade shows that in all seven countries of the region there is *no sufficiently high coverage of therapy* and *insufficient* effectiveness of *therapy*, with regards to the suppression of viral load. Speaking of the "coverage of therapy" indicator, it should be recognized that in recent years many countries have managed to significantly increase the absolute number of people receiving ARV therapy. Particularly impressive is the growth in the number of patients in the Russian Federation. However, due to the high rate of spread of the epidemic (high morbidity rates) in percentage terms, the coverage rate remains low. The analysis of national policies to fight the epidemic of HIV infection in general demonstrates the commitment of countries to the concept of *test and treat*, i.e. the total therapy coverage.

The therapy effectiveness indicator is actively discussed as a matter of the 90x90x90 concept. Effectively working patient registries are required in order to comprehensively estimate the concept. Such registries are maintained in countries where GF programs operate; in the Russian Federation, the work is currently underway to implement a single national registry, which will enable to more accurately estimate what percentage of patients in the Russian Federation have suppressed viral load as a result of therapy. As noted above, low rates of suppressed VL may indicate the need of additional work on patient counseling and on monitoring adherence to therapy, as well as, where necessary, optimizing treatment regimens (introducing options with fewer side effects, combination drugs).

2 Conclusion 2. Inflated prices from domestic producers

The analysis of prices shows that the policy of supporting national manufacturers in the field of public procurement leads to an unjustified inflation of prices for drugs and, as a result, restriction of access. This is most evident in the example of Belarus and Kazakhstan. In Kazakhstan, based on the analysis, an action plan was developed to optimize costs, taking into account the inflated prices for drugs supplied by the domestic manufacturer. The policy of supporting domestic manufacturers also exists in the Russian Federation, with the so-called "odd one out" rule (prohibiting the participation of foreign manufacturers in tenders if there are at least two producers from the EEU). However, this does not lead to such an obvious overpricing, perhaps because of the larger number of competing firms and the need to provide therapy with a much larger number of patients. Also in the Russian Federation, the project on monitoring the prices of ARV drugs by the patient community has been operating for 8 years already, and this issue has received increasing attention in recent years from relevant agencies, such as the Federal Antimonopoly Service.

3 Conclusion 3. Patent barriers cause high prices

The analysis of prices and comparison of price information with information on the presence or absence of patents make it clear that patents are certainly the cause of overpricing (among other reasons, see the conclusion about domestic manufacturers). This thesis is clearly illustrated by the prices of tenofovir/emtricitabine and dolutegravir. Prices for original products in countries where there is a patent are several times higher than the prices for generic products of this drug. Traditionally expensive are the patented second and third line drugs (lopinavir/ritonavir, rilpivirine, raltegravir, darunavir). The presence of a patent for ritonavir prevents the procurement of combination generics (atazanavir/ritonavir and darunavir/ritonavir), when it appears on the market. In fact, a patent for one drug limits the use of a whole class of PI. Considering the fact that many patents are granted by Eurasian Patent Organization and cover several countries in the region, coordinated actions in this area are important.

4 Conclusion 4. Efavirenz and lopinavir/ritonavir are dominant

The analysis of procurement structure shows that the most popular base drugs are efavirenz 600 mg (for the first line) and lopinavir/ritonavir (for the second line). In this case, lopinavir/ritonavir in a number of countries gets a very large share of the budget (from 20% to 50%).

5 Conclusion 5. Dolutegravir at the start

In the latest WHO recommendations, including the guide to switching to new drugs, special attention is paid to dolutegravir. Ukraine became the first country (out of seven countries covered by the analysis), which began to use the dolutegravir relatively widely. The table below shows that at least Armenia, Moldova, Kyrgyzstan and Ukraine have the opportunity to introduce generic drugs at low prices. In particular, these countries can apply the dolutegravir/tenofovir/lamivudine combination, the estimated price of which is $75 per patient a year (in Moldova and Ukraine, including royalties).

It is worth noting that at the time of writing of this report, there appeared the data that may indicate an increased risk of fetal defects during pregnancy when using dolutegravir. Currently WHO, EMA, FDA and BHIVA have issued statements that do not recommend dolutegravir to women who are planning to become pregnant, and recommend switching from dolutegravir to women in the first trimester of pregnancy. At the moment, there is no exact knowledge how this will affect the deployment of programs to expand access to ARV therapy in the region.

6 Conclusion 6. Extremely limited selection of options in the second and third line in 2017

An analysis of the procurement structure also shows that, apart from Russia, atazanavir and darunavir are not used anywhere else, despite the fact that Armenia, Belarus, Kyrgyzstan, Kazakhstan, Moldova and Ukraine[9] have the right to procure atazanavir generics. One possible explanation for the limited use of atazanavir is the patents for ritonavir, which block the combination of atazanavir and ritonavir from entering the market. As a protease inhibitor, atazanavir is usually used in combination with pharmacokinetic enhancers: either ritonavir or cobicistat. All countries covered in the study, with the exception of Russia, have the right to supply generic cobicistat, but the problem is that the generic cobicistat has not yet entered the market.

"Second generation" non-nucleoside reverse transcriptase inhibitors (etravirine, rilpivirin) and the integrase inhibitor raltegravir are also practically not used. Due to patent protection, the prices for these drugs are very high.

The limited choice of second-line drugs may be one of the reasons for the relatively low efficacy of therapy, which can be seen from the results of the analysis of "cascades". There is a possibility that in some cases first-line drugs may be used, to which patients have already developed resistance. A more detailed analysis of the situation of primary resistance in countries is needed.

In addition, the limited choice may be one of the reasons for the situation in Kazakhstan, where more than 11% of patients receive regimens consisting of 3 NRTIs, which contradicts international standards.

7

Conclusion 7. Most countries have opportunities to deliver generics of innovative drugs to the market in the near future.

The table below shows that in the perspective of several years, all countries covered by the study (with the exception of the Russian Federation) will have the opportunity to introduce generic inhibitors of integrase (elvitegravir and bictegravir), as well as the combination of atazanavir and cobicistat. In case of elimination of the patent barrier associated with darunavir, it is also possible to introduce a generic combination of darunavir/cobicistat, when/if it comes to the market. The widespread use of the second generation non-NRTIs remains questionable due to high prices and patent barriers.

[9] Ukraine was included in the license of Patent Pool in 2017; until then there existed atazanavir-related patent barriers.

Table 7. The ability to supply generics of second and third line drugs in seven EECA countries under the terms of licensing agreements

	ATV	DTG	BIC	TAF	COBI	EVG
Armenia		Yes	Yes	Yes	Yes	Yes
Belarus		No	Yes	Yes	Yes	No
Kyrgyzstan		Yes	Yes	Yes	Yes	Yes
Kazakhstan		No	Yes	Yes	Yes	Yes
Moldova		Yes	Yes	Yes	Yes	Yes
Russia	Generics are in the market	No	No	No	No	No
Ukraine		Yes	Yes	Yes	Yes	Yes

8

Conclusion 8. Almost all countries prefer to use combination drug forms.

A significant and striking exception to this rule is Russia, where less than 1% of patients receive entire-regimen-in-one-tablet drugs. In Belarus, in 2017, relatively few patients received drugs containing the entire regimen in one tablet, but a very large percentage of patients received NRTI combination base, and in 2018 the number of patients on the three-drugs-in-a-tablet regimen should grow, according to the preliminary analysis.

9

Conclusion 9. Countries are beginning to use the services of international procurement agencies and international organizations (UNICEF) in procurement at the expense of national budgets

One of the goals is to achieve the lowest possible prices for drugs. In 2017, this method was used by Ukraine and Kazakhstan, and as the comparative analysis of prices demonstrates, it proved its effectiveness. In Kyrgyzstan, the legislation was amended to allow procurement at the expense of the state budget through international procurement agencies. The procurement method through national tenders is more expensive, especially if there are provisions that give preferences to national producers during the bidding process.

10

Conclusion 10. Countries are beginning to take the path of simplifying drug registration.

Simplified registration mechanisms exist at least in Ukraine, Kyrgyzstan, Moldova and Armenia, and in Armenia, amendments to the legislation were made at the end of December 2017. As the analysis of legislation shows, for the application of a simplified and accelerated procedure it is normally enough that the drug is registered in one of the countries with strict regulatory authorities (traditionally in USA, EU, Japan and, in some cases, other countries).

11

Conclusion 11. Treatment Standards according to WHO

Generally, countries are guided by WHO guidelines when developing national guidelines, in some cases cautiously looking towards more “advanced guidelines” of DHHS and EACS. The implementation of DHHS and EACS recommendations is hindered by the absence of a number of drugs on the market and the inflated prices for some key drugs.

Areas of Work for the Future

The areas of work can be divided into two blocks: *regional areas*, which can, to varying degree, apply to all countries covered by this report and not only by this report, and *country-specific areas*, which are more characteristic of certain countries (although they can touch other countries, should the situation change). Country recommendations are described in detail in the national reports, and here we give only a few examples. To a greater extent, we will focus on the trends peculiar to the entire region.

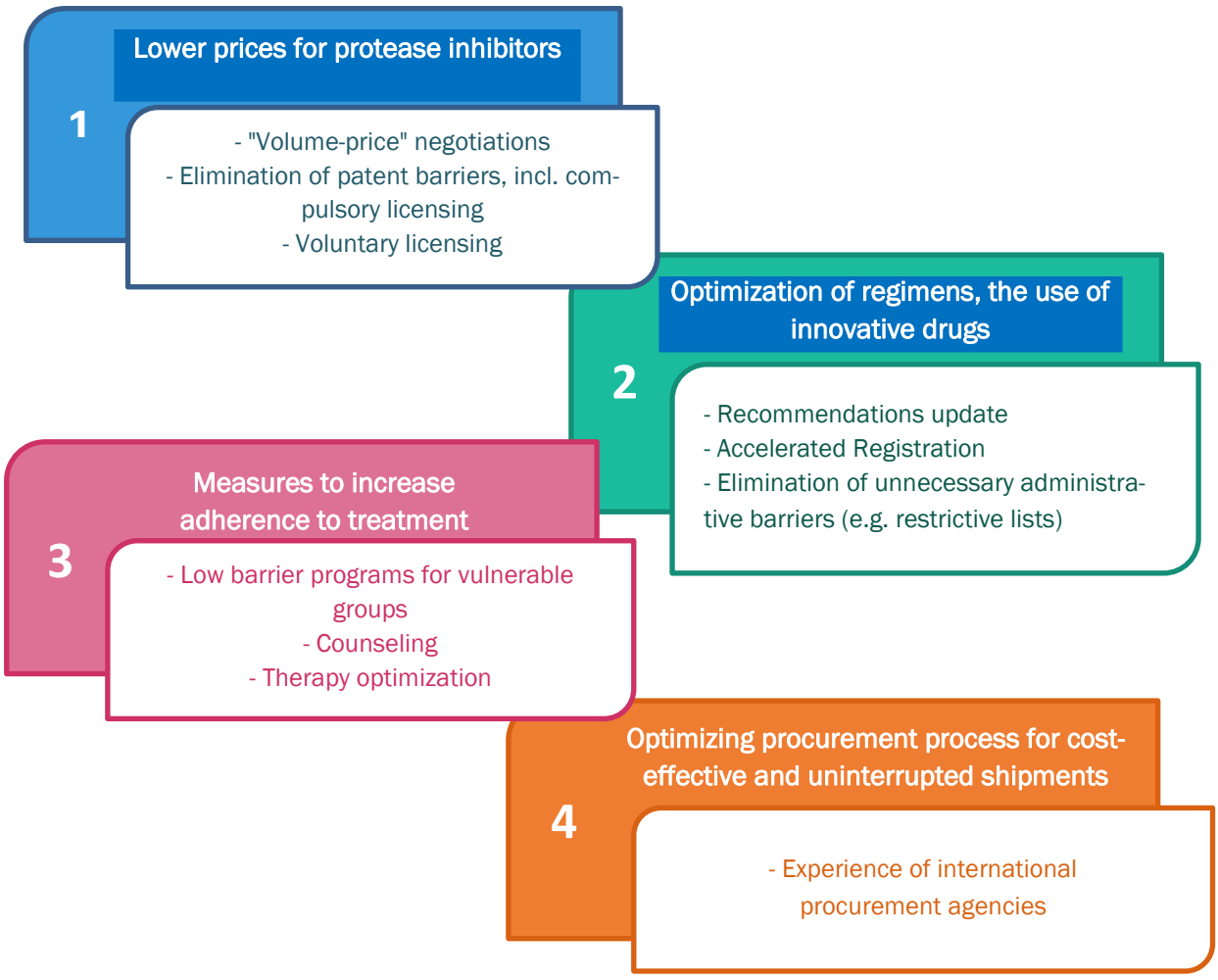
- **Expanded access by reducing the prices for patented drugs:**
    - Negotiations with patent holders on the inclusion of countries in the territory of license agreements or on the refusal of prosecution of patent rights in the country. This work, in particular, is carried out in relation to dolutegravir in Russia, Belarus and Kazakhstan; these three countries are not included in the territory of the license agreement, and, therefore, are not entitled to supply cheap generics.
    - Negotiations with patent holders to reduce prices and expand access to the drug. Again, this strategy can be used in relation to dolutegravir and other patented drugs (for example, raltegravir) in the Russian Federation, Belarus and Kazakhstan.
    - Elimination of patent barriers, either by disputing issued patents, using the power of the law, or by issuing compulsory licenses. Among the drugs for which such measures can be applied, ritonavir, lopinavir, dolutegravir, darunavir, rilpivirine, raltegravir, tenofovir/emtricitabine should be noted. Strategies will vary from country to country and from drug to drug, depending on each specific case. In particular, challenging patents for lopinavir/ritonavir is already occurring in Ukraine, and may become relevant for countries such as the Russian Federation, Belarus, Kazakhstan and Kyrgyzstan. If negotiations on patent rights or price cuts for dolutegravir fail, then countries can use a compulsory licensing strategy.

- **Expanding the access through therapy regimen optimization:**
    - Replacing more expensive and older options with newer and cheaper ones. This strategy may be relevant in situations where new options with the same, or often higher, efficiency and safety, that available in the form of generics or at a special price program in the form of originals, may turn out to be cheaper than the options already used. In this case, the possibility of using the strategy of replacing one option to another can be considered. In particular, dolutegravir in the form of generics may be cheaper than the efavirenz and lopinavir/ritonavir already used, and atazanavir/ritonavir or darunavir may be cheaper than lopinavir/ritonavir. This work should be carried out in close collaboration with clinicians in order to cater to the needs of patients in the best way.

- **Procurement system optimization to reach a lower level of prices and uninterrupted supply:**
    - The experience of Ukraine and Kazakhstan has shown that the use of international procuring agencies is a relevant option for achieving the lowest possible prices and, as a result, saving the budget and freeing up funds to procure more drugs. Countries such as Armenia, Moldova, Kyrgyzstan and Belarus, which to some extent are already procuring drugs at state expense or are planning to do it in the near future (Kyrgyzstan) should consider using this option and, if necessary, optimize the legislation accordingly. Such work, in particular, is already underway in Kyrgyzstan.

- **Increase efficiency of therapy through various methods, including regimens optimization and improving the work in the area of adherence**

  - Low rate of suppressed VL as a result of therapy is alarming. More research is required to get a better picture, for example, on the level of adherence and resistance. In any case, countries should systematically work on optimization of regimens, not only with the purpose of saving, but also with the goal of improving treatment standards. The analysis shows that, in particular, in the Russian Federation, combination drugs are not used at all, in Kazakhstan a large percentage of patients receive the regimens of 3 NRTIs, and in general, a very small percentage of patients in the region receive second and third line drugs.



Conclusions on the project implementation

The results of the project, first of all, showed that non-governmental organizations in the region dealing with HIV infection have all the necessary potential to implement similar projects for monitoring the availability of drugs. In this case, most of the work on the collection and analysis of data can be carried out within the organization, with the exception of certain highly specialized areas (for example, the interpretation of legislation or statistical data processing).

This “learning by doing” is extremely important for further dialogue with government officials: it provides a deep understanding of the problems and, in some situations, provides a unique expertise that can be used as a weighty argument in the negotiations.

The project also demonstrated the effectiveness of the dialogue between the patient community and the state, built on the basis of the conducted (in some cases, jointly) analytical work. The working meetings, during which the conclusions and recommendations on the results of the reports were discussed, were not declarative, but quite practical, in some cases they resulted in actions aimed at eliminating the gaps stated in the reports. In order to be effective in the long term, the project must function systematically and continuously.