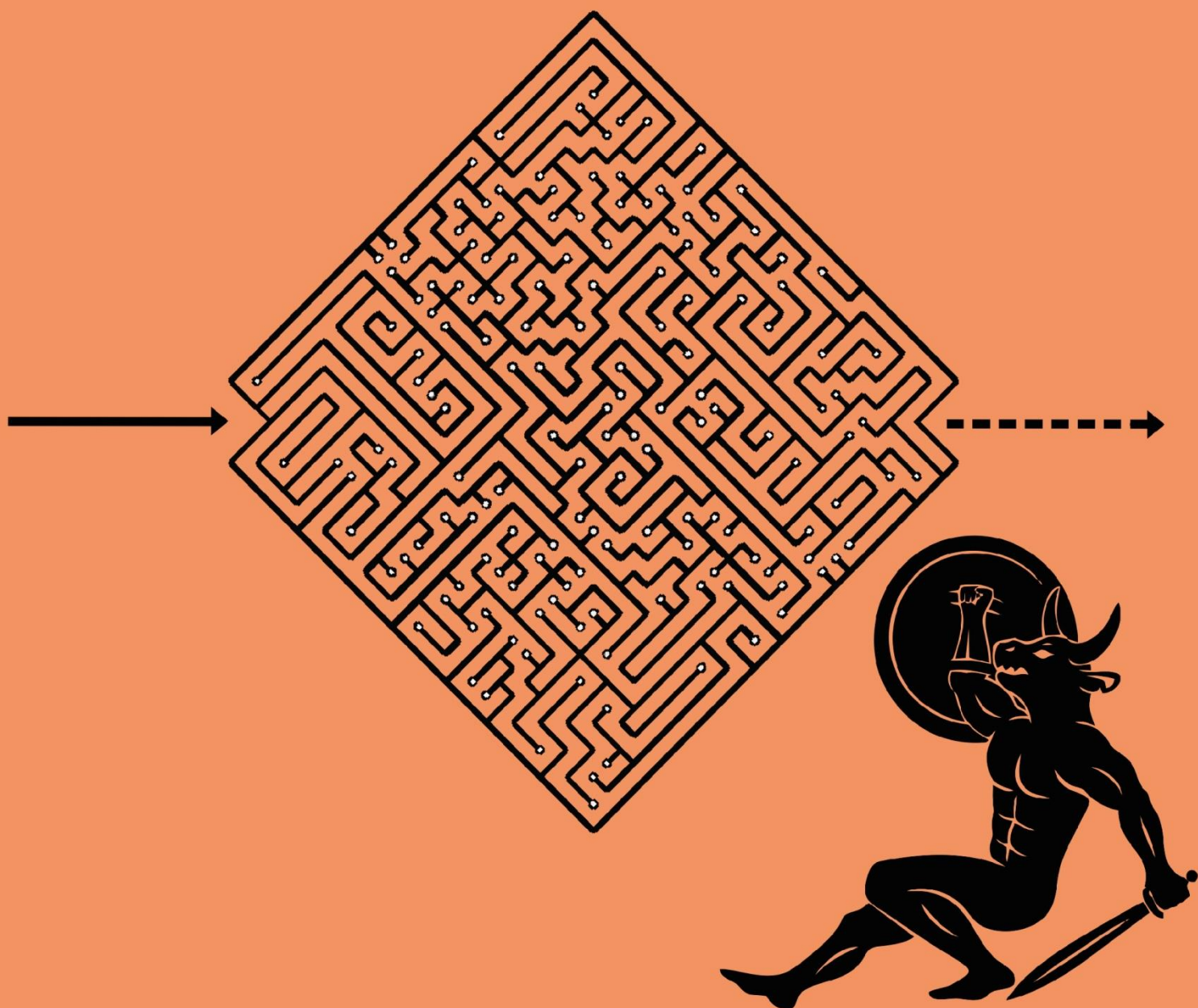


Exit from the labyrinth: the end of decentralization

The results of monitoring of purchases of ARV drugs in Russia in 2016



WRITING TEAM AND ACKNOWLEDGMENTS

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The mention of any treatment regimens in the text of the report under no circumstances can be used as an alternative to consulting a medical professional.

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LIST OF ABBREVIATIONS

ARV, ART - antiretroviral drugs
HIV - Human Immunodeficiency Virus
WHO - World Health Organization
UIS - Unified Information System
VED - List of Vital and Essential Drugs
II - integrase inhibitors
TIN - Taxpayer Identification Number
PI - protease inhibitors
Ministry of Health - Ministry of Health of the Russian Federation
INN - international non-proprietary name
NRTI - nucleoside reverse transcriptase inhibitors
NtRTI - nucleotide reverse transcriptase inhibitors
IMP - initial maximum price
NNRTI - non-nucleoside reverse transcriptase inhibitors
PL - compulsory license
TN - trade name
POA - public online auction
RF - Russian Federation
AIDS - Acquired human immunodeficiency syndrome
FAS - Federal Antimonopoly Service of the Russian Federation
FZ - federal law

INTRODUCTION

In 2016, the epidemiological situation of HIV infection continued to worsen: the trend of increasing new cases and deaths among HIV-infected patients persisted.

According to preliminary data¹, as of 31.12.2016, the total number of Russians with HIV infection reached 1,114,815 people, 243,863 of them died for various reasons. In 2016, dispensary observation in specialized medical institutions covered 675,403 people, which amounted to 77.5% of 870,952 people living with the diagnosis of HIV infection.

The number of new infections in 2016 was 103,438 people, with the exception of those found anonymously and foreign citizens. Of those infected, 31,284 people died for various reasons in 2016, which is 13.5% more than in 2015. The growth rate of the incidence of new cases and deaths in the last three years is shown in the diagram below.

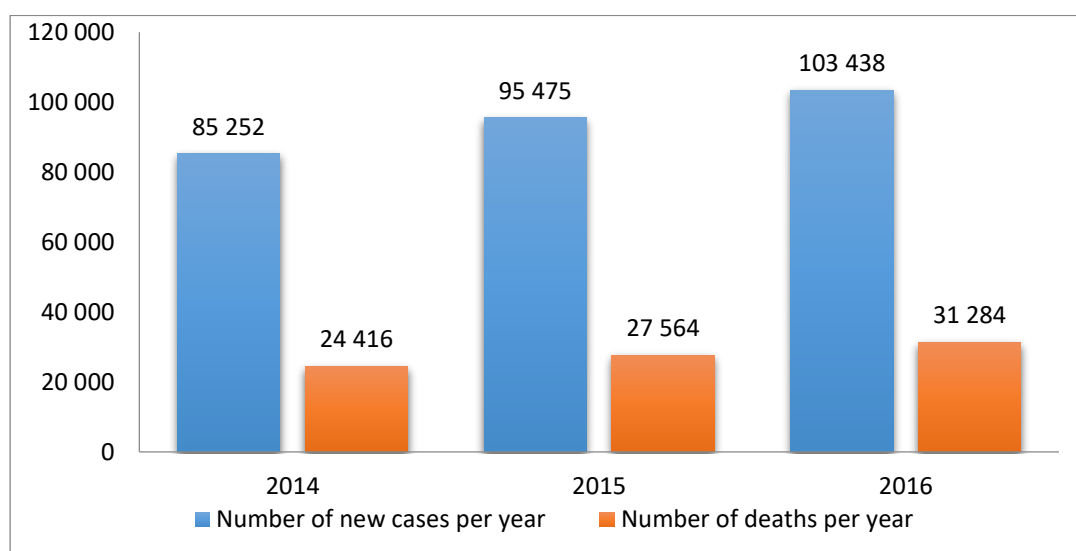


DIAGRAM 1. GROWTH RATE OF NEW CASES OF HIV INFECTION AND MORTALITY AMONG HIV-INFECTED PEOPLE IN THE RUSSIAN FEDERATION IN 2014-2016

Most cases of infection in 2016 occurred due to injecting narcotics with non-sterile instruments (48.8%) and heterosexual intercourse (48.7%).

The prevalence of HIV infection (the registered number of people living with HIV, among the entire population) as of December 31, 2016 was 594.3 per 100 thousand. High prevalence of HIV infection (more than 0.5% of the total population) is registered in the 30 largest regions where 45.3% of the country's population lived as of December 31, 2016.

¹ The fact sheet "HIV infection in the Russian Federation as of December 31, 2016" prepared in the Federal Scientific and Methodological Center for the Prevention and Control of AIDS of the Federal Central Research Institute of Epidemiology of Rospotrebnadzor (Russian Agency for Health and Consumer Rights) based on the form of monitoring of Rospotrebnadzor

According to official data², ARV therapy in 2016 was available to 285,920 patients, that is, treatment coverage was 32.8% of the number of registered patients with HIV infection or 42.3% of those registered on dispensary.

According to the Global HIV Strategy "90-90-90" adopted by UNAIDS, at least 90% of people living with HIV should be provided with antiretroviral therapy to stop the HIV epidemic. It means that **that the number of people needing treatment in Russia can reach 800,000 people, that is, about 500,000 people do not receive the necessary therapy at the moment.**

² The fact sheet "HIV infection in the Russian Federation as of December 31, 2016" prepared in the Federal Scientific and Methodological Center for the Prevention and Control of AIDS of the Federal Central Research Institute of Epidemiology of Rospotrebnadzor based on the form of monitoring of Rospotrebnadzor

The purpose of the report is to obtain conclusions based on the analysis of public procurement monitoring data for ARV drugs in 2016, and to develop recommendations for improving the situation with drug provision in the Russian Federation.

The main stages of writing the report:

1. Development of the research concept

The base of legislative and normative legal acts in the sphere of procurement in the Russian Federation and the specifics of their application in the practice of procurement of ARV drugs has been studied.

The main quantitative and qualitative markers for further study were defined.

2. Search and collection of information

The objects of research and further analysis included information on purchases carried out under Federal Law No. 44-FZ dated April 5, 2013, "On the contract system in the sphere of procurement of goods, works, services for ensuring state and municipal needs" and Federal Law No. 223- FZ dated 18.07.2011 "On the procurement of goods, works, services by certain types of legal entities".

The collection of primary information was performed in real time by monitoring of auction documents posted on the public (open) part of the website of the Unified Information System in the field of procurement www.zakupki.gov.ru.

The system approach developed, reference and information systems and computer technologies were used for the formalized qualitative and quantitative analysis of documentation and systematization of the received data. During the data collection and analysis, auctions as of December 31, 2016 were taken into account at all stages of the procurement (placement of an order) for the period December 1, 2015 through December 31, 2016, with the exception of auctions for 2015 completed in 2015 and auctions for 2017 announced in 2016.

To search and identify the required auctions in the procurement register, the following search requests were used:

- International non-proprietary names (INN) of drugs for the treatment of HIV infection in accordance with Government Decree No. 1438 dated February 27, 2012, as amended on May 29, 2015, and the grls.rosminzdrav.ru register, as well as their word forms;
- Taxpayer identification numbers (TIN) and other requisite details for AIDS centers and infectious diseases clinics that provide HIV treatment services in constituent entities of the Russian Federation, as well as regional health departments and other procurement authorities;

- the terms "antiretroviral drugs", "HIV", "HIV infection", "drugs" and their forms;
- the code according to OKPD-2 (All-Russian Product Classifier by Economic Activities) "Antiviral Drugs for Systemic Use".

In each of the found auctions, the main objects for studying were auction documents published on the website in the word, excel, pdf, etc. formats.

The methods of justifying the initial maximum price (IMP), the protocols of reviewing applications for participation in the auction and summarizing the results, information on payments and the object of procurement, contracts, information on the execution (termination) of the contract were analyzed.

3. Further processing of data

Key indicators for further study and analysis were identified, the necessary qualitative and quantitative characteristics for each auction, essential for research and subsequent analysis and generalization were structured.

The data for each region has been summarized into separate tables. All information received by regions was grouped and integrated into a single data set, which was edited, verified and standardized for further formalized processing and analysis.

For the statistical analysis, the QlikView business analysis system was used. The methods included data modification, descriptive statistics, classification and identification of objects, frequency analysis, contingency tables, interrelation of values, graphic images of statistical information. After processing, the data array was reported as Microsoft Office Excel spreadsheets. For the analysis and evaluation of the values identified and the parameters considered, the following characteristics obtained as a result of statistical analysis were used:

- Determination of absolute, average and percentage (share), minimum and maximum values of the parameters studied;
- Comparison of values of the parameters studied, mean values and maximum deviations in the current period;
- Time series;
- Comparative values of the parameters studied, according to the results of previous monitoring.
- Systematization of identified qualitative problems.

4. Preparation of the final analytical report

The following data were used in the report:

- Minimum and maximum cost of the drugs (price dispersion among the regions);
- Weighted average cost of the drugs;
- Proportion of the drugs (based on one year treatment course and expences) in the total volume of purchases, by INN and trade names (TN);
- The timing of the announcement of auctions;

- The percentage of failed and canceled auctions from the total number of auctions included in the sample;
- The connection between the failure of auctions and the delivery of drugs;
- Distributors which win auctions in the constituent entities of the Russian Federation;
- The presence of competition in the auction;
- The amount of money for purchasing ARV drugs;
- Proportion of generic/original drugs in procurement;
- Number of one year treatment courses for drugs of various groups;
- Proportion of drugs included/not included in the VED list.

According to the above methodology, 4,493 auctions for the supply of antiretroviral drugs (ARVs) conducted in 85 regions of the Russian Federation by various purchasers, as well as auctions conducted by the Ministry of Health of the Russian Federation for institutions of federal subordination were found and analyzed.

The main emphasis in the analysis was made on the successful auctions (total 3735 auctions) with the status of "execution completed" and "ongoing".

To compare and evaluate the data obtained, comparable data of the following reports was used:

- Treatment Preparedness Coalition: Procurement of ARVs in 2014: a chronicle of decentralization. The results of monitoring purchases and provision of ARV drugs in the Russian Federation. St. Petersburg, 2015. Second edition (15.06.2015);
- Treatment Preparedness Coalition: Procurement of ARVs in 2015: Theory of relativity. Results of monitoring purchases of ARV drugs in the Russian Federation. St. Petersburg, 2016. First edition (28.04.2016).

Current versions of the publications are available on the website <http://itpcru.org>.

Data on the maximum permissible prices for VED drugs in the regions are taken from the site <http://www.ros-med.info/>

PRICING IN THE RUSSIAN FEDERATION

In RF, state regulation of prices is carried out only for drugs included in the VED List, which contains most ARV drugs. Prices are regulated by the following:

- Approving the methodology for establishing maximum selling prices by manufacturers for drugs included in the VED List;
- state registration of the maximum selling prices for drugs established by the manufacturers included in the VED List;
- maintenance of the state register of the manufacturers maximum selling prices for drugs included in the VED List;
- establishing by the subject of the Russian Federation the maximum sizes of wholesale and retail mark-ups to actual selling prices established by manufacturers.

For drugs not included in the VED List, the price is not subject to government regulation and is formed only by the principle of market competition.

Since a purchaser in public procurements may only purchase medicines based on the INN, and within one INN, there are usually several TN of the drug registered, then the maximum selling prices of manufacturers may differ.

TABLE 1. REFERENCE COUNTRIES FOR DETERMINING THE SELLING PRICE FOR MEDICINAL PRODUCTS INCLUDED IN THE VED LIST IN THE RUSSIAN FEDERATION

1. Country of manufacture			
2. Belarus	3. Denmark	4. The Netherlands	5. Turkey
6. Belgium	7. Ireland	8. Poland	9. Ukraine
10. Bulgaria	11. Spain	12. Portugal	13. France
14. Croatia	15. Italy	16. Romania	17. Czech Republic
18. Greece	19. Kazakhstan	20. Slovakia	21. Hungary
22. Other countries			

The approved maximum selling prices of manufacturers are entered in the state price register, which is available on the website www.grls.rosminzdrav.ru

ARV DRUGS IN THE RUSSIAN FEDERATION

A. APPROVED DRUGS

As of 31.12.2016, 32 INNs (107 TNs) were approved in the Russian Federation without taking into account various strengths and dosage forms.

In 2016, only one new drug for the treatment of HIV infection with INN tenofovir/emtricitabine/efavirenz 300/200/600 mg (TN Atripla) was approved.

The list of medicinal products subject to procurement for federal budget funds is defined in Decree No. 1438. All drugs indicated in the Decree are also included in the VED List.

In December 2015, a new VED List for 2016 was approved, which, in comparison with the previous version, included another drug for HIV treatment, namely emtricitabine/rilpivirin/tenofovir 200/25/300 mg. This is the first drug with a "one pill once a day" regimen, approved in the Russian Federation. However, the drug was not included in the updated draft Decree No. 1438, so in 2016 it could not be purchased for the federal budget.

In 2016, 60 INNs were purchased for the federal budget. Drugs not included in the VED List and in Decree No. 1438 were purchased at the expense of regional and municipal budgets.

In 2016, VED list for 2017 did not include any of the drugs for the treatment of HIV infection submitted to the approval committee, and subsequently the RF Ministry of Health "froze" the List and left it unchanged. Thus, the list of VED did not include the drugs for the treatment of HIV infection: emtricitabine, tenofovir/emtricitabine, dolutegravir, maraviroc, raltegravir chewable tablets. At the same time, indinavir and nelfinavir which are not purchased and not used for several years remained in the list.

As will be shown below, the absence of drugs in the VED List directly affects their availability.

B. STRUCTURE OF PURCHASING ARVS IN 2016

In 2016, 64.46% of the budget for ARV drugs were spent on the purchase of five drugs:

- **Lopinavir/ritonavir tablets 200/50 mg, 100/25 mg, solution for oral administration 60 ml** – 6,088,069,201.49 rubles (27.27%)
- **Raltegravir tablets 400 mg, chewable tablets 25, 100 mg** – 2,300,195,855.08 rubles (10.30%)
- **Atazanavir capsules 150, 200, 300 mg** – 2,214,073,807.34 rubles (9.92%)
- **Darunavir tablets 400, 600, 800 mg** – 2,053,895,812.92 rubles (9.20%)
- **Etravirine tablets 100, 200 mg** – 1,736,017,364.57 rubles (7.78%)

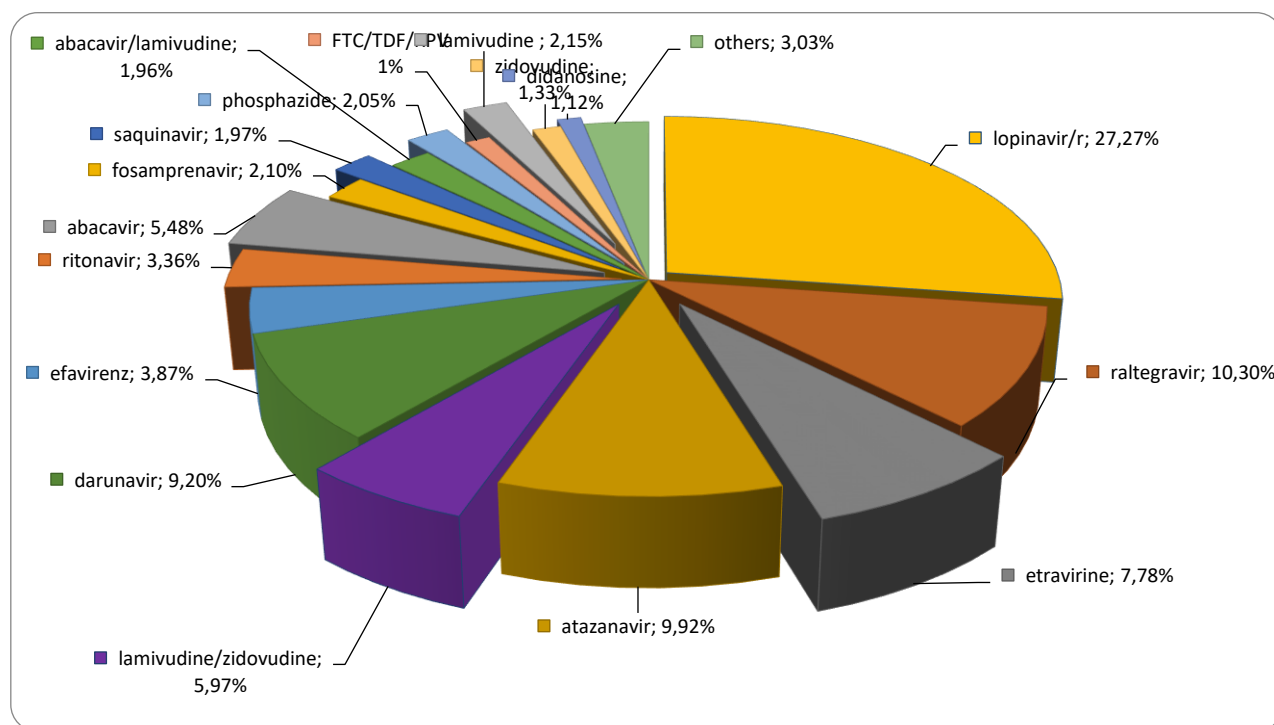


DIAGRAM 2. DISTRIBUTION OF THE BUDGET FOR ARVS, BY INN, %

Based on the number of patients who could potentially receive therapy during 365 days, the most popular drugs were:

In the group of third (or backbone) drugs:

- Efavirenz 100, 200, 600 mg - 93 702 courses of therapy
- Lopinavir/ritonavir 200 + 50 mg - 65 132 courses
- Atazanavir 150, 200 and 300 mg - 23 514 courses
- Nevirapine 200 mg - 11 964 courses
- Etravirine 100, 200 mg - 7 509 courses

In the group of NRTIs:

- Lamivudine 150, 300 mg - 145,823 courses
- Lamivudine/zidovudine - 79 396 courses
- NRTIs that do not contain lamivudine:
- Tenofovir 300 mg - 48 343 courses
- Abacavir 150, 300 and 600 mg - 46 707 courses
- Zidovudine 100, 300 mg - 20 358 courses

NRTI group drugs

Given that, in accordance with international and Russian guidelines, lamivudine or emtricitabine should be present in the backbone NRTI combinations in almost all cases, we counted lamivudine (and emtricitabine) as a separate drug for the calculation of the share of the most popular NRTIs, and added the number of courses of combination drugs containing lamivudine or emtricitabine to the corresponding second drugs. The results are shown in the diagram below.

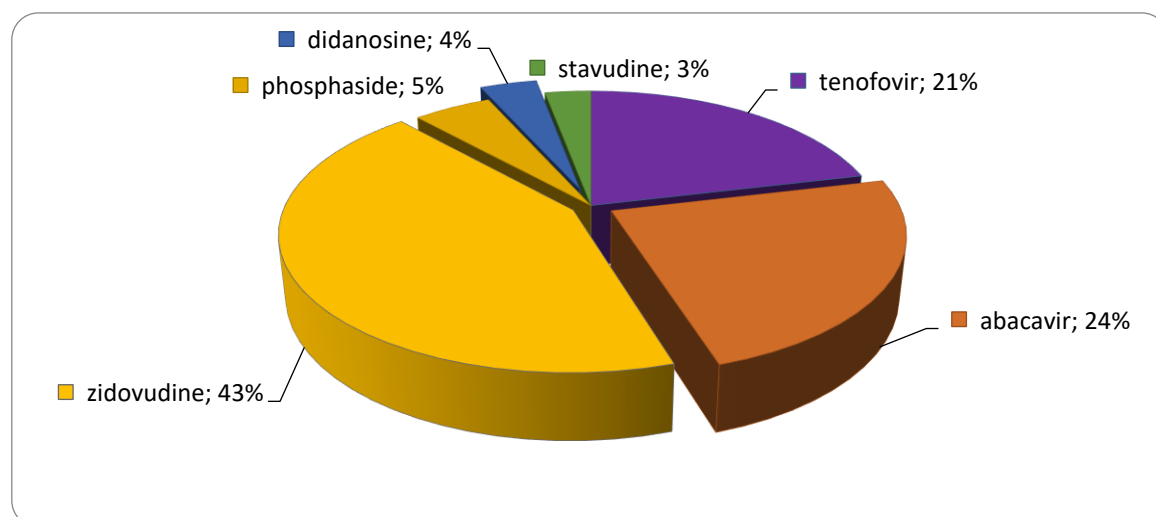


DIAGRAM 3. SHARES OF DRUGS IN THE GROUP OF NIOT BASED ON THE CALCULATION OF NUMBER OF ONE YEAR COURSES MINUS LAMIVUDIN AND EMTRICITABINE AS MONO-COMPONENT PRODUCTS, NOT INCLUDING PEDIATRIC FORMS³

Compared to the previous year, the share of abacavir did not change, the share of zidovudine decreased by 16%, the share of stavudine, phosphazide and didanosine slightly decreased (by 1% for each drug). The share of tenofovir increased from 2% last year to 21% in 2016, which is associated with a significant reduction in the price of this drug. It should be noted that the combined preparations of tenofovir/emtricitabine and tenofovir/emtricitabine/rilpivirin are practically not available and the drug tenofovir/emtricitabine/efavirenz is completely unavailable. That is, an increase in the availability of tenofovir occurred only due to tenofovir as a mono-component product.

Third drugs

The most purchased third drugs included efavirenz (41%, its share increased by 7%), lopinavir/ritonavir (29%, its share decreased by 6% compared to the previous year) and atazanavir (10%, its share decreased by 3%).

³ The share of abacavir includes abacavir/lamivudine, of zidovudine - lamivudine/zidovudine, of tenofovir - tenofovir/emtricitabine, tenofovir/emtricitabine/efavirenz combination products

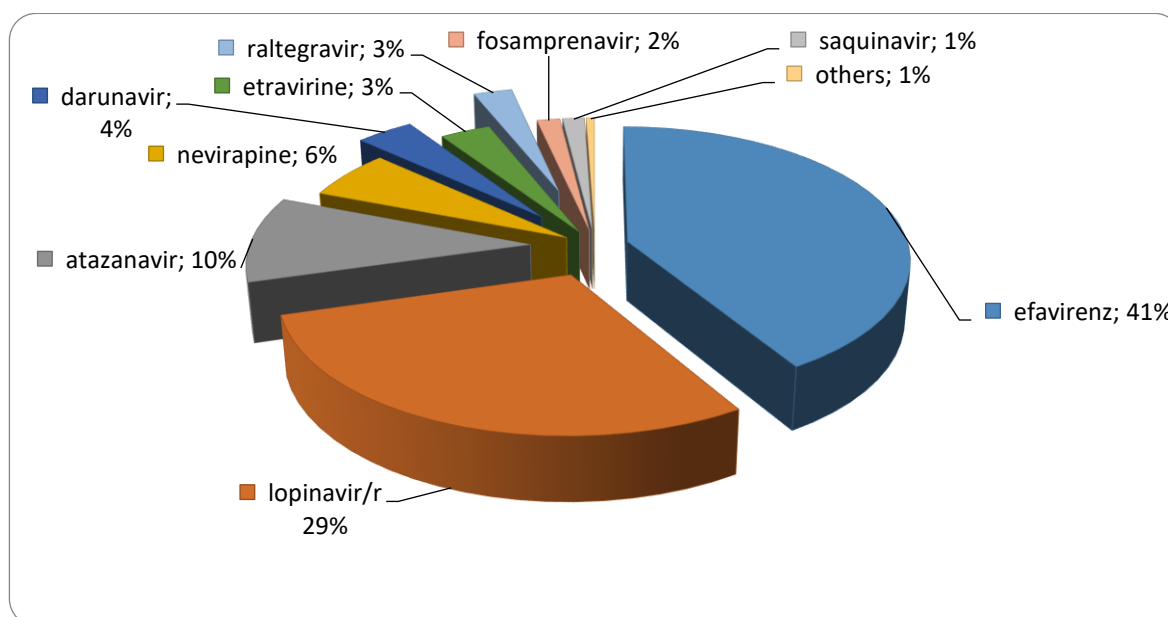


DIAGRAM 4. SHARES OF DRUGS IN THE GROUP OF THIRD DRUGS

Budget allocation between different drug groups

Like last year, **more than 70% of the federal budget for ARV therapy has been spent on the so-called third drugs**. Of the five drugs that account for the largest amounts in the budget structure, four belong exactly to this group (lopinavir/ritonavir, darunavir, raltegravir, atazanavir). For three drugs (lopinavir/ritonavir, raltegravir, atazanavir) there are no generic drugs.

Drugs that comprise a complete regimen in one tablet ("three drugs in one") account for about 1% of the budget, and less than 1% of patients receive such regimens. Compared to the previous year, these indicators remained unchanged.

MONO-COMPONENT DRUGS

Tenofovir. In 2016, there was a turning point in access to treatment with regimens containing tenofovir. The problem of limited access to this drug remained one of the most urgent and debated problems in the field of drug provision for HIV-positive patients in Russia since 2011⁴.

The cost of one-year treatment course with tenofovir dropped within three years by almost 30 times.

TABLE 2. WEIGHTED AVERAGE PRICE FOR A PACKAGE OF TENOFOVIR, 300 MG, IN 2014-2016, RUBLES.

Weighted average price per pack for 2014, rubles.	Weighted average price per pack for 2015, rubles.	Weighted average price per pack for 2016, rubles.	The most common price in purchases in 2016, rubles.
9,064.01	7,069.80	1,081.20	350.00

It should be noted that all tenofovir purchased was generic (TNs "Tenofovir" and "Tenofovir-TL"), the original tenofovir was not purchased in 2016.

Due to the cardinal price reduction, the volume of purchases of tenofovir 300 mg in 2016 increased significantly. The sum of all contracts was 201,469,328.15 rubles; 48,343 one-year courses of tenofovir were purchased.

If only 2.52% of patients took tenofovir-containing regimens in 2015, in 2016 the number of such patients increased almost 10-fold due to the increased volume of purchases of tenofovir 300 mg.

Abacavir. Another drug, for which in 2016 a significant reduction in price was reported, is abacavir tablets in strengths of 150 and 300 mg. The price of abacavir 600 mg practically did not decrease, possibly because the drug in such strength is only produced by one manufacturer.

The cost of one pack of abacavir 300 mg decreased three-fold during the year: the average weighted price per pack in 2015 was 4,191 rubles, and in 2016 it was 1,671.60 rubles.

Nevirapine. A significant reduction in the price was also recorded for nevirapine. The weighted average price for one pack of nevirapine 200 mg in 2015 was 1,024 rubles, in 2016 the price dropped to 470.40 rubles.

Stavudine. Despite the fact that the WHO protocols recommend "to stop the use of stavudine in first-line regimens due to its generally recognized metabolic toxicity"⁵, purchases of stavudine in 2016 continued.

⁴ <http://itpcru.org/2011/11/09/obrashhenie-s-prosboj-vklyuchit-v-zhnvlp-tenofovir/>; <http://itpcru.org/2015/02/10/sbor-podpisej-organizatsij-dostup-k-tenofoviru-v-rf/>

⁵ Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. World Health Organization. June 2013.

The purchases has slightly decreased compared to 2015. The one-year course costs 27,856.80 rubles for stavudine 30 mg and 38,361.50 rubles for stavudine 40 mg. The one-year course of tenofovir costs 300 mg is 3,701.10 rubles, and of zidovudine 300 mg - 11,833.30 rubles. The cost for stavudine 30 and 40 mg was 176,733,586.10 rubles.

DRUGS NOT INCLUDED IN THE VED LIST

In 2016, nine out of ten INNs not included in the VED List were purchased (dolutegravir 50 mg, lamivudine/zidovudine/nevirapine 150/300/200 mg, maraviroc 150 and 300 mg, raltegravir 25 and 100 mg, rilpivirine 25 mg, tenofovir/emtricitabine/efavirenz 245/200/600 mg, tipranavir 250 mg, emtricitabine/tenofovir/rilpivirine 200/300/25 mg, emtricitabine 200 mg).

The amount spent for the purchase of these drugs was 493,709,162.41 rubles (2.21% of the total budget for ARVs). Compared to the previous year, this amount increased 3.5-fold.

The number of one-year courses of drugs not included in VED, increased almost five-fold (to 3,214). The most purchased drugs were lamivudine/zidovudine/nevirapine tablets 150/300/200 mg (1 401 one-year courses), emtricitabine/tenofovir/rilpivirin 200/300/25 mg (789 one-year courses), raltegravir chewable tablets 100 mg (287 courses).

FIXED-DOSE COMBINATIONS

The World Health Organization recommends using combination drugs administered one tablet once a day to begin treatment. According to the results of studies, combination drugs facilitate adherence to treatment, increasing the convenience of administration, and also minimizing the probability of medication error⁶.

As of December 31, 2016, four drugs were registered in the Russian Federation, which are a complete regimen in one tablet: abacavir/lamivudine/zidovudine (TN Trizivir), lamivudine/zidovudine/nevirapine (TN Zidolam-N), tenofovir/emtricitabine/efavirenz (TN Atripla), emtricitabine/rilpivirin/tenofovir (TN Eviplera). Also, three combination drugs of two NRTIs are available in the Russian Federation: lamivudine/zidovudine, abacavir/lamivudine, tenofovir/emtricitabine.

Compared to the previous year, the volume of purchases of two drugs, Eviplera and Zidolam-N, has significantly increased in 2016. Trizivir, as well as Atripla, were not purchased in 2016.

TABLE 3. PURCHASES OF FIXED-DOSE COMBINATIONS IN 2015-2016

TN	Number of one-year courses, 2015	Number of one-year courses, 2016
Trizivir	7	0
Zidolam-N	185	1,401
Atripla	-	0
Eviplera	55	789
Total	247	2,190

The number of patients who could receive 3-in-1 drugs increased in 2016 and amounted to 2,190 people (0.83% of the total estimated number of people taking ARV drugs). In 2015, this number was 249 patients (0.16% of the total estimated number). Despite the almost 5-fold increase in the purchase of 3-in-1 drugs in 2016, their share in the total amount of all medicines purchased remained insignificant.

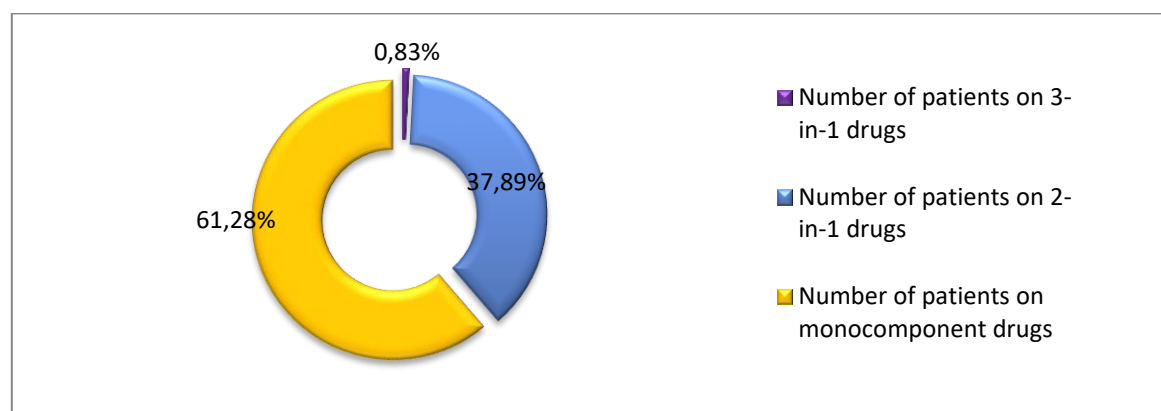


DIAGRAM 5. SHARE OF COMBINATION DRUGS AND THE SHARE OF MONOCOMPONENT DRUGS IN THE GENERAL AMOUNT (IN ONE-YEAR COURSES)

⁶ A selection of studies is available on the website of the Treatment Preparedness Coalition, <http://itpcru.org/2014/01/20/kombinirovannye-preparaty-patsienty-skoree-za/>

PEDIATRIC DOSAGES AND FORMS

Pediatric forms of drugs include strengths and dosage forms that imply convenient reception for children of younger age group (syrups, solutions, powders, suspensions). As of December 31, 2016, 13 such products of various forms and strengths have been approved in the Russian Federation, but only 9 drugs of those were purchased in 2016.

A total of 154,077 packs of pediatric ARVs were purchased. The number of one-year courses of preparations (syrups, solutions, powders and suspensions) was not counted, since the recommended daily dosage depends on the weight of the child and is calculated individually.

The share of pediatric forms of the total sum of all contracts concluded was 1.28% (311,568,746 rubles).

The prices for pediatric products in 2016 remained practically unchanged. This is primarily due to the lack of generics in the Russian market.

It should be noted that 2016 was a record year for failed auctions for pediatric forms (almost 36% of all auctions for pediatric forms). The main reason is the absence of participants for bidding.

NUMBER OF PATIENTS ON ART

According to international and Russian guidelines, antiretroviral therapy regimens should consist of three drugs: two backbone drugs of the nucleoside/nucleotide reverse transcriptase (NRTI) class and a third drug of the class of non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (IIs), CCR5 inhibitors. As a rule, two NRTI drugs should include either lamivudine or emtricitabine. This rule may not apply to the so-called third-line regimens or reserve regimens, the selection of which is carried out individually.

The authors of the report made approximate estimations of the potential number of patients who could receive therapy, based on data on procurement of ARV drugs for 2016. For this purpose, all ARV drugs were divided into three groups:

- backbone drugs - NRTIs
- "third drugs" - NNRTIs, PIs, IIs, CCR5 inhibitors
- other drugs - combination drugs "3-in-1", a complete regimen

The drug ritonavir, which is used only as a pharmacokinetic enhancer in combination with protease inhibitors was accounted separately in the analysis.

Calculation of the number of treatment courses was carried out according to the so-called "optimistic scenario": by adding half of the simple sum of all one-year courses of mono NRTIs, plus the sum of all strengths of combination drugs with two NRTIs, minus the recommended and permissible combinations of drugs.

The drugs that make up the third component of ARV therapy (PIs, NNRTIs, IIs, etc.) were summarized (taking into account the need for boosting by ritonavir) based on daily dosages in accordance with the guidelines. The sum of drugs of this group was compared with the amount of NRTIs, for the verification of data.

Drugs that represent a complete treatment regimen (abacavir/lamivudine/zidovudine, abacavir/lamivudine/nevirapine, tenofovir/emtricitabine/rilpivirin) were added to the sum of "third drugs" based on daily dosages in accordance with the guidelines.

The calculation was based on the amount of third drugs, because, in accordance with the current Russian guidelines for the treatment of patients with HIV infection in 2015 ⁷ and the recommendations of the European AIDS Clinical Society (EACS) in 2016 ⁸, under certain conditions, the use of regimens containing only PI, boosted with ritonavir, or regimens containing a PI plus one NRTI.

Below is the share of third drugs (NNRTIs, PIs, IIs, etc.) in purchases in 2016, in terms of the number of patients.

⁷ <http://itpcru.org/2016/01/13/rossiya-novye-natsionalnye-rekomendatsii-po-dispansernomu-nablyudeniyu-i-lecheniyu-bolnyh-vich-infektsiei/>

⁸ <http://www.eacsociety.org/files/guidelines-8.1-russian.pdf>

TABLE 4. SHARE OF THIRD DRUGS (NNRTI, PI, II, ETC) IN PURCHASES IN 2016 IN TERMS OF THE NUMBER OF PATIENTS

INN	Estimated number of one-year courses, 2016	Share of each drug
Efavirenz tab. 600 mg	92,601.58	41.18%
Lopinavir/ritonavir 200/50 mg	65,132.28	28.97%
Nevirapine 200 mg	11,964.58	5.32%
Atazanavir caps. 300 mg	4,463.92	1.99%
Etravirine tab. 200 mg	7,491.56	3.33%
Darunavir tab. 400 mg	3,402.74	1.51%
Saquinavir tab. 500 mg	3,252.04	1.45%
Atazanavir caps. 200 mg	14,213.37	6.32%
Fosamprenavir tab. 700 mg	3,415.81	1.52%
Raltegravir tab. 400 mg	5,602.78	2.49%
Efavirenz tab. 200 mg	491.78	0.22%
Raltegravir tab. chewable 100 mg	286.93	0.13%
Dolutegravir tab. 50 mg	182.22	0.08%
Rilpivirin tab. 25 mg	141.78	0.06%
Raltegravir tab. chewable 25 mg	42.33	0.02%
Tipranavir caps. 250 mg	43.64	0.02%
Maraviroc tab. 150 mg	19.73	0.01%
Lopinavir/ritonavir 100/25 mg	1,253.10	0.56%
Efavirenz tab. 100 mg	609.19	0.27%
Maraviroc tab. 300 mg	19.07	0.01%
Enfuvirtide 90 mg/ml	31.81	0.01%
Darunavir tab. 600 mg	3,216.00	1.43%
Etravirine tab. 100 mg	18.08	0.01%
Atazanavir caps. 150 mg	4,836.86	2.15%
Darunavir tab. 800 mg	2,126.88	0.95%
Total	224,860.05	100%

List of NRTIs by the volume of purchases presented as the number of patients:

TABLE 5. ESTIMATED NUMBER OF PATIENTS RECEIVING VARIOUS NRTIS IN PURCHASES IN 2016

INN	Estimated number of one-year courses, 2016	Estimated number of one-year courses, taking into account the coefficient, 2016
Abacavir/lamivudine tab. 600/300 mg	8,466.25	8,466.25
Abacavir tab. 150 mg	608.14	304.07
Abacavir tab. 300 mg	27,899.88	13,949.94
Abacavir tab. 600 mg	18,199.70	9,099.85
Didanosine caps. 125 mg	117.62	58.81
Didanosine caps. 250 mg	2,431.73	1,215.86
Didanosine caps. 400 mg	6,115.38	3,057.69
Zidovudine caps. 100 mg	340.27	170.14
Zidovudine tab. 300 mg	20,018.51	10,009.25
Lamivudine/Zidovudine 150/300 mg	79,396.36	79,396.36
Lamivudine tab. 150 mg	113,676.62	56,838.31
Lamivudine tab. 300 mg	32,147.15	16,073.58
Stavudine caps. 30 mg	6,312.47	3,156.23
Stavudine caps. 40 mg	571.66	285.83
Tenofovir/emtricitabine 300/200 mg	193.56	193.56
Tenofovir tab. 300 mg	48,343.01	24,171.51
Phosphazide tab. 200 mg	10,102.70	5,051.35
Phosphazide tab. 400 mg	1,648.60	824.30
Emtricitabine caps. 200 mg	153.45	76.73
Total	NA	232,399.61

The list of the "complete one-pill regimen" drugs with an indication of the estimated number of patients is given in the table below.

TABLE 6. SHARE OF "COMPLETE ONE-PILL REGIMEN" DRUGS IN PURCHASES IN 2016 AS THE NUMBER OF PATIENTS

INN	Estimated number of patients, 2016	Share for each drug, %	Estimated number of patients in 2016 and 2015, the difference
Lamivudine/zidovudine/nevirapine	1,401.37	63.97%	+ 1,215.78
Emtricitabine/tenofovir/rilpivirin	789.45	36.03%	+ 734.38
Abacavir/zidovudine/lamivudine	0.00	0.00%	-7.89
	2,190.82	100.00%	-

Thus, based on the analysis of the structure of procurement of ARV drugs in Russia in 2016, it can be seen that the share of "complete one-pill regimen" drugs in purchases in 2016 as the number of patients is 100.00%.

oncluded that **the purchased amount of drugs covers approximately 227 thousand patients**. It is important to note that this figure does not include patients taking pediatric forms of drugs (because of the impossibility of accurate calculating the number of regimens).

This analysis does not take into account the situations where patients begin treatment and interrupt it for whatever reason. The extremely limited distribution of adherence programs, especially those aimed at vulnerable groups, a lack of specialists, limited resources, in our opinion, makes such a factor as the refusal of therapy the most likely reason for the discrepancy between the official number of patients on treatment and the number of courses declared in this report.

THE COST OF ARVS IN PURCHASES IN 2016

In 2016, unlike the previous two years, for the first time there was a decrease in the average prices for most ARV drugs (an average of 8%).

The largest decrease in prices compared to the previous year was for the following drugs:

- Tenofovir tablets 300 mg (-85%)
- Abacavir tablets 300 mg (-60%)
- Nevirapine tablets 200 mg (-54%)
- Emtricitabine/rilpivirin/tenofovir tablets 200/25/300 mg (-49%)
- Dolutegravir tablets 50 mg (-47%)
- Abacavir tablets 150 mg (-36%)
- Abacavir tablets 600 mg (-27%)

The drugs, the price for which has grown most significantly:

- Tipranavir capsules 250 mg (+ 26%)
- Zidovudine capsules 100 mg (+ 18%)
- Etravirine tablets 100 mg (+ 12%)

Prices for pediatric forms of the drugs decreased by an average of 3%, and this also occurred for the first time in three years of decentralized procurement of ARV drugs. The price has changed most significantly for the following drugs:

- Fosamprenavir suspension for oral administration 225 ml (-7%)
- Zidovudine solution 200 ml (-6%)
- Lamivudine solution 240 ml (-6%)

ANALYSIS OF PRICES FOR DRUGS IN DIFFERENT CLASSES

NRTIS

The diagram below shows the weighted average prices for the recommended daily dosage for NRTIs (the most commonly purchased strengths). Compared to the previous year, the price difference within one class of drugs has significantly decreased, but still remains big: the price for the most expensive and the cheapest drug within one class in 2016 differed 12-fold (compared to 26-fold last year).

It is noteworthy that for the drugs, the price for which practically did not change compared with the previous year (didanosine 400 mg, zidovudine 300 mg and stavudine 30 mg), several generics were purchased in 2016. The question why the price did not decrease (and, in the case of stavudine, even grew) remains open.

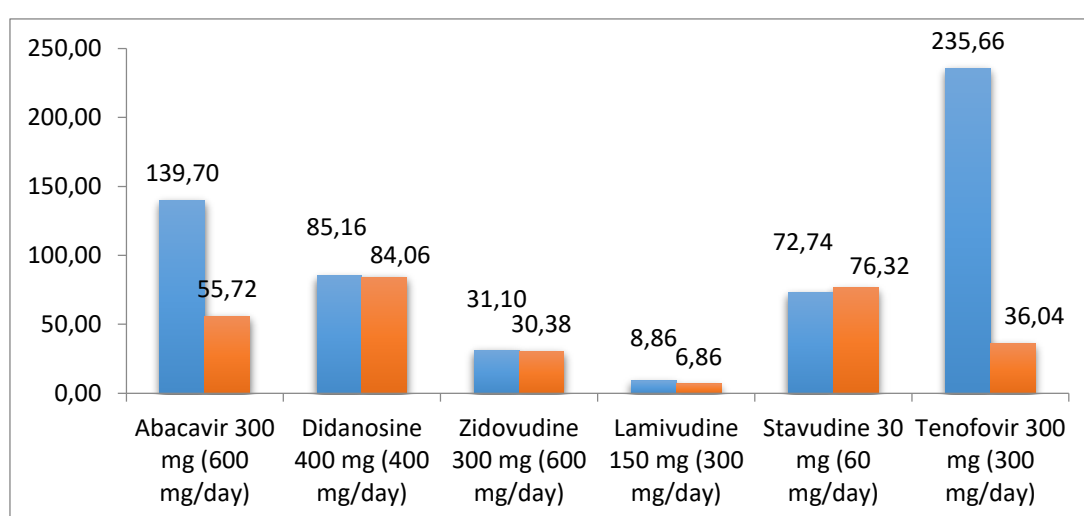


DIAGRAM 6. WEIGHTED AVERAGE PRICES FOR THE RECOMMENDED DAILY DOSE FOR DRUGS FROM THE NRTI CLASS IN 2015-2016

In 2016, there were also cases when the price of generic was higher than that of a branded drug. This situation was noted in the purchases of didanosine 250 mg and 400 mg (the price of generic exceeded the price of the original drug by 1-2%).

NNRTIS

When analyzing prices for NNRTIs, there is a significant difference between the price of the so-called "second generation" NNRTIs (rilpivirin, etravirine) and the "first generation" NNRTIs (nevirapine, efavirenz). Compared to last year, the price of drugs of this class has not actually decreased, and in the case of efavirenz 600 mg - even increased (+5%). It is important to note that rilpivirin is not included in the VED List and the price for it is not regulated.

Like in the previous year, the price for generic efavirenz 600 mg was 65% higher than that of the original drug. This situation, according to the authors of the report, is illogical and unacceptable in the context of improving access to treatment through the introduction of generics.

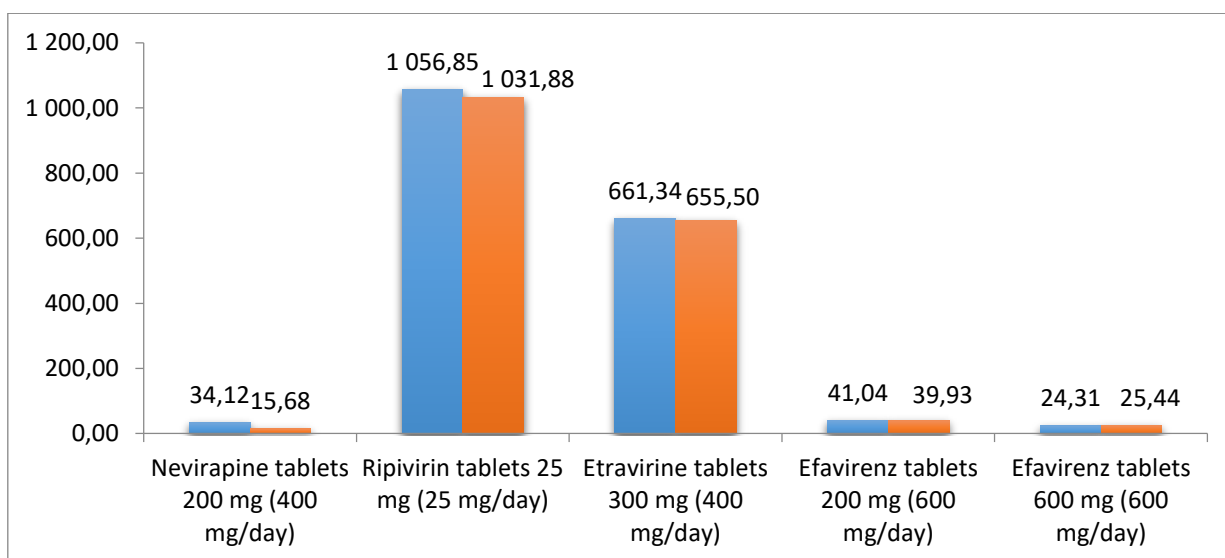


DIAGRAM 7. WEIGHTED AVERAGE PRICES FOR THE RECOMMENDED DAILY DOSE FOR DRUGS FROM THE NNRTI CLASS

PI

The greatest variance in prices for drugs of the PI group included in the VED List, like in the previous year, is 4-fold. A separate case is tipranavir, which is purchased in very limited quantities and not included in the VED List. It is worth noting that the price for it increased by 26% in 2016.

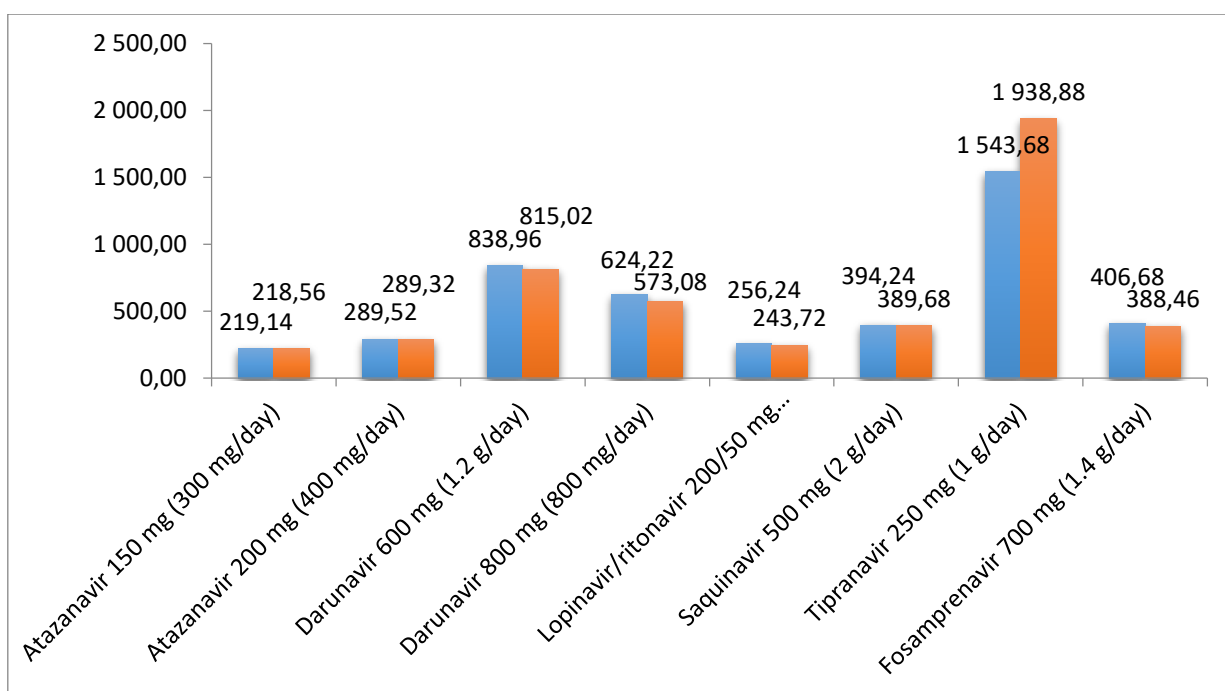


DIAGRAM 8. WEIGHTED AVERAGE PRICES FOR THE RECOMMENDED DAILY DOSE FOR DRUGS FROM THE PI CLASS

In this group of drugs, the only approved generic products are available for darunavir 600 and 800 mg; the generics were cheaper than the original by 8-16%.

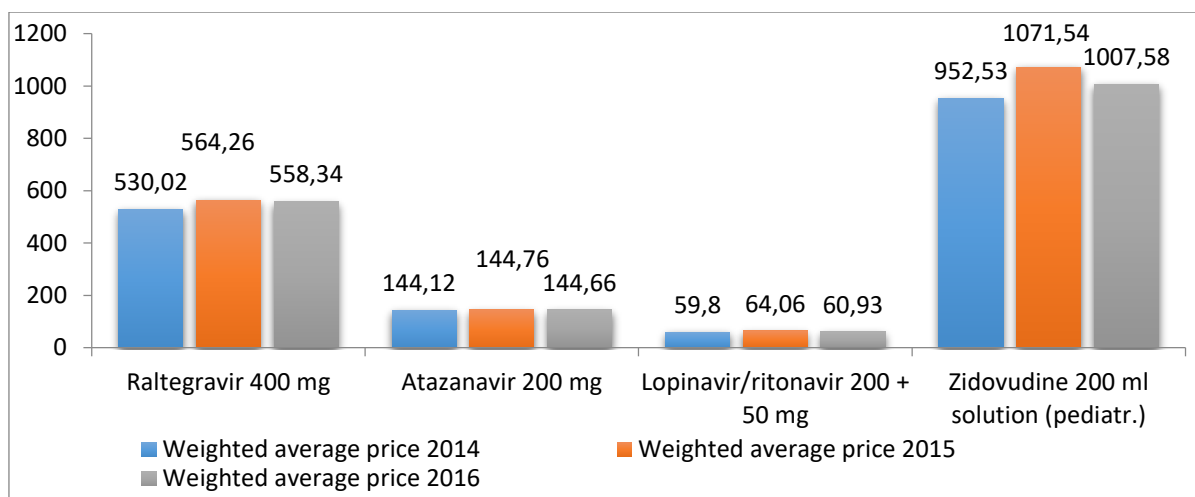


DIAGRAM 1. PRICES FOR INDIVIDUAL DRUGS WHICH HAVE NO GENERICS APPROVED IN RF IN 2014-2016, RUBLES PER UNIT.

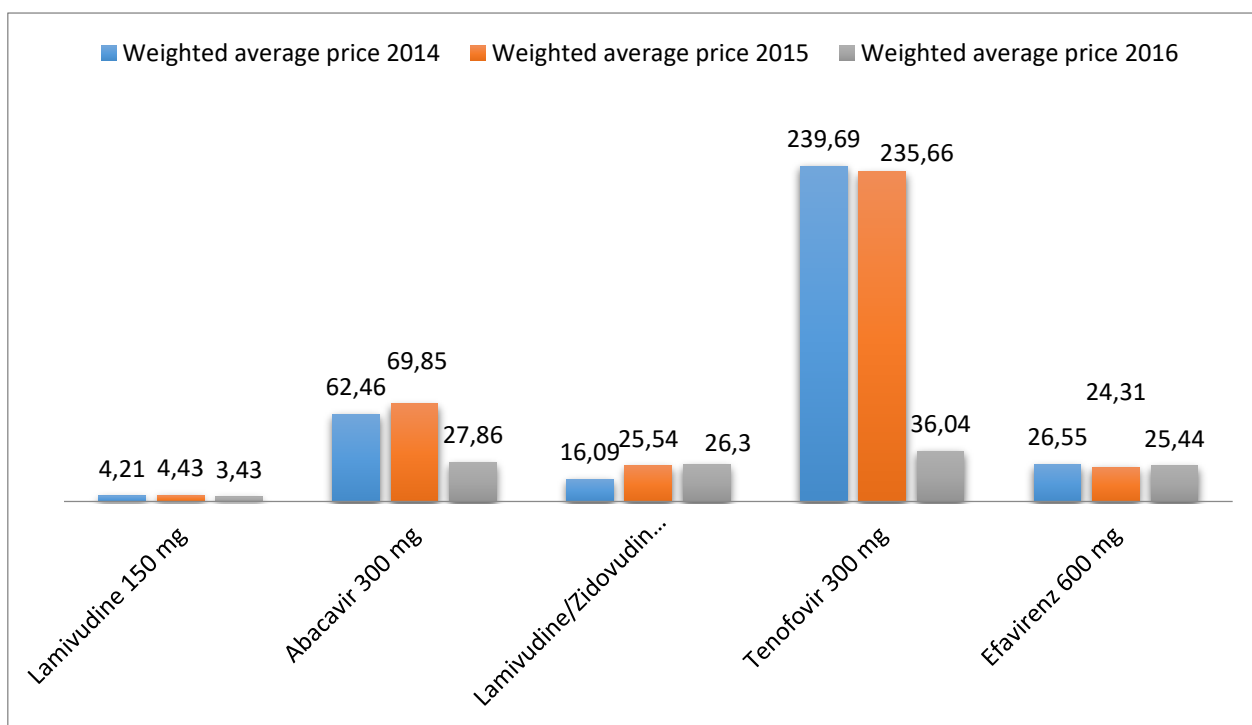


DIAGRAM 2. PRICES FOR INDIVIDUAL DRUGS WHICH HAVE GENERICS APPROVED IN RF, IN 2014-2016, RUBLES PER TABLET.

* Lamivudine 150 mg: 9 analogues, abacavir 300 mg: 2 analogs, lamivudine/zidovudine 150/300 mg: 8 analogues, tenofovir 300 mg: 4 analogues, efavirenz: 3 analogues.

As can be seen from the diagrams above, prices for products which have no generics that have a monopoly position on the market continue to remain stably high, while prices for those which have generics drop mostly (tenofovir, abacavir). In the conditions of a shortage of vital therapy and limited resources for the purchase of drugs, it is recommended to consider a set of measures to reduce prices for patented drugs, starting from direct negotiations with manufacturers to voluntary or compulsory licenses.

COST OF THE MOST USED TREATMENT REGIMENS IN RUSSIA IN 2016

Based on the procurement data, the most commonly used first-line treatment regimens in 2016 were:

- Tenofovir + lamivudine + efavirenz
- Lamivudine/zidovudine + efavirenz (lamivudine + zidovudine + efavirenz)
- Abacavir/lamivudine + efavirenz (abacavir + lamivudine + efavirenz)
- Zidovudine + lamivudine + nevirapine

The most commonly used second-line regimens were those containing lopinavir/ritonavir and atazanavir + ritonavir.

As can be seen in the diagrams below, the cost of the most common first-line regimens significantly decreased compared to the previous year, mainly due to a significant decrease in the cost of tenofovir, abacavir and nevirapine. It is worth noting that the cost of the second-line regimens has changed mainly due to decreased prices for tenofovir and abacavir.

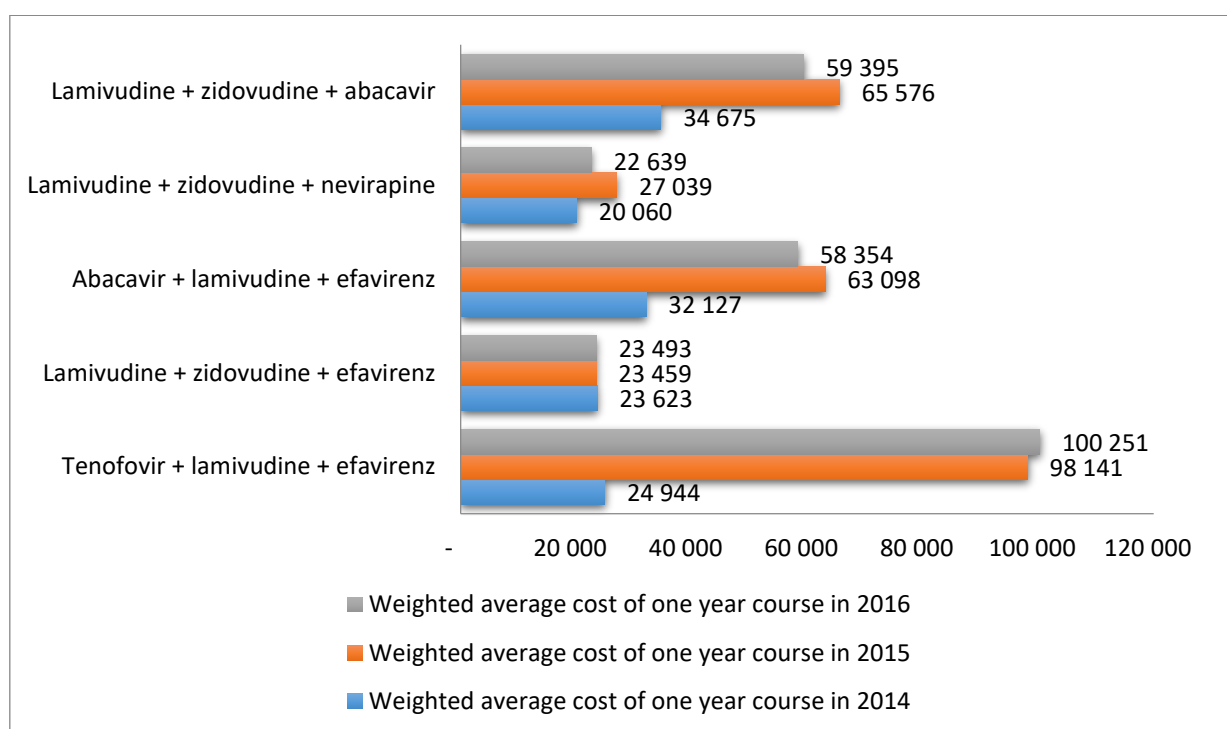


DIAGRAM 3. WEIGHTED AVERAGE COST OF THE FIRST-LINE TREATMENT REGIMENS IN RF IN 2014-2016

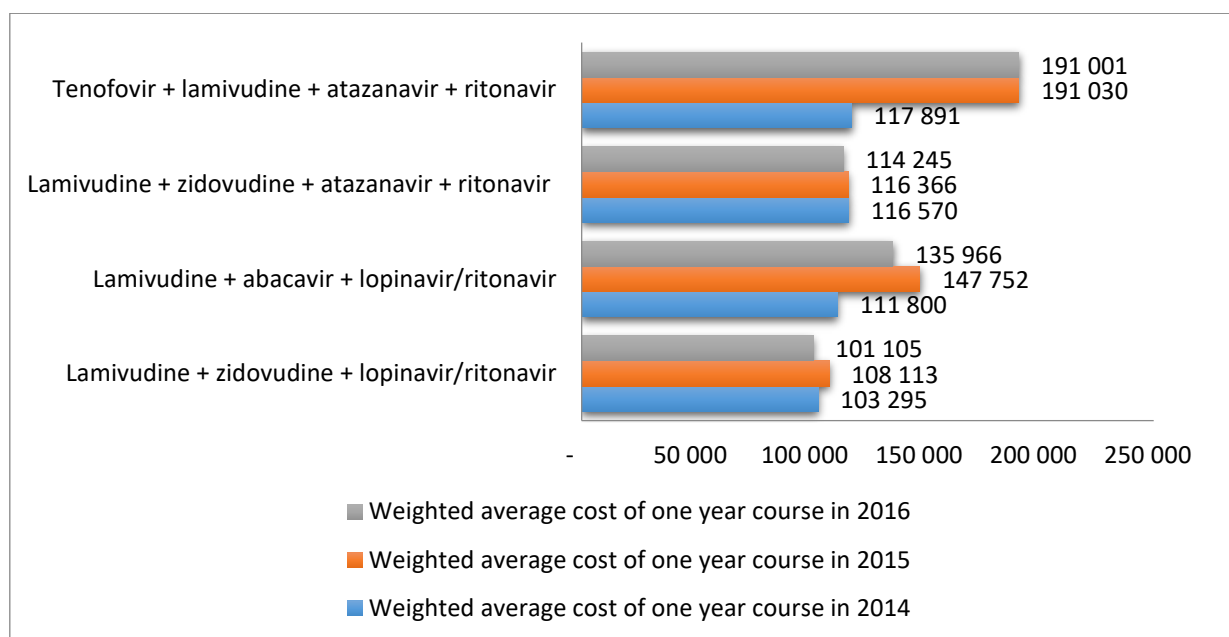


DIAGRAM 4. WEIGHTED AVERAGE COST OF THE SECOND-LINE TREATMENT REGIMENS IN RF IN 2014-2016, RUBLES.

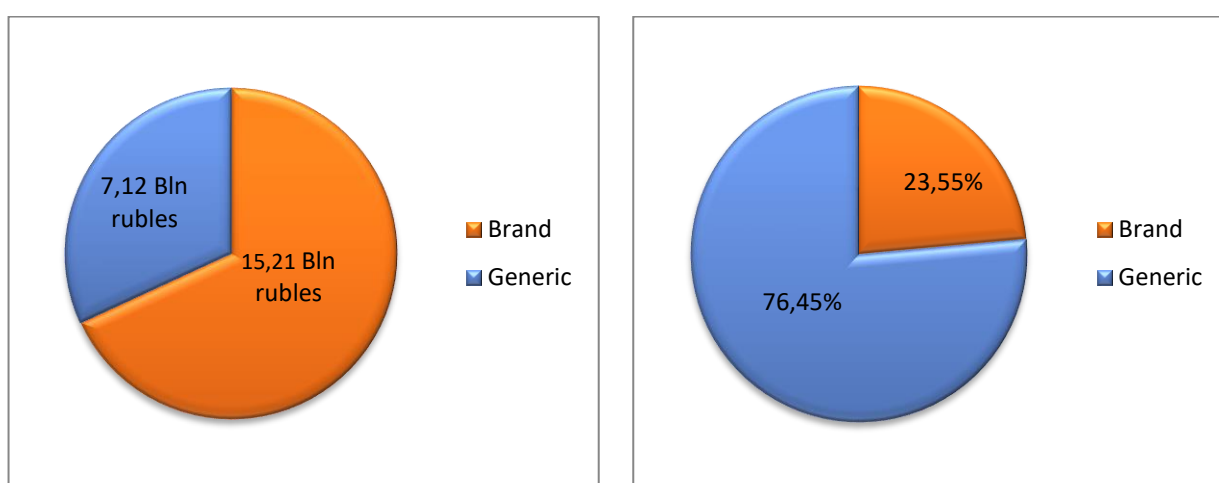
RATIO GENERIC/ORIGINAL IN THE PROCUREMENT OF ANTIRETROVIRALS

In RF, 30 TNs of original ARVs and 78 TNs of generic ARV drugs are approved (the amount is calculated without the dosage forms and strength of one drug). In 2016, 25 TNs were purchased of all approved original products, and 32 TNs of all generic drugs.

The share of original drugs in the total amount of concluded contracts was 68.12% (15,208,702,511.65 rubles), the share of generics was 31.88% (7,118,087,655.22 rubles)..

At the same time, in terms of the potential number of one-year courses, the share of original drugs accounted for 23.55%, and for generic drugs - 76.45%.

Fig. A) The brand/generic ratio presented in money terms and B) presented as the number of courses



74.22% of the amount spent on original drugs, or 11,288,942,684 rubles, were spent for four drugs in different strengths: lopinavir/ritonavir, raltegravir, etravirine, atazanavir. More than half of all spent funds for the purchase of ARV drugs in 2016 (55.27%) were spent for these drugs, which are part of the treatment regimen for almost a third of all patients.

CONCLUSIONS

1. The approximate number of patients that could be provided with therapy in 2016 based on the procurement analysis data is approximately 227,000 people. Taking into account the pediatric forms and the possible error in the identification of auctions, the total number of patients may be **about 235 thousand**. This is more than 50 thousand more than in 2015. This figure is confirmed by interviews with independent experts. The difference between the figure declared by Rospotrebnadzor of 286 thousand people and the figure of 235 thousand people may be partly explained by low adherence and discontinuation of therapy (statistics include all patients who took at least one tablet). In addition, in the absence of a single federal register, there may also be errors related to internal migration and registration of patients in other regions.
2. **The number of people who do not receive therapy at the moment may amount up to 500 thousand people.** To achieve the 90-90-90 target, the number of patients on therapy should be increased at least three-fold.
3. There was a significant increase in the number of patients receiving tenofovir-containing regimens (12.5-fold). Almost 50 thousand people could receive such regimens in 2016. The growth was due to the dropped prices for tenofovir in the mono-component form. Thus, the clinical practice of treating HIV infection in Russia with regard to the use of tenofovir is approaching international standards.
4. The total budget for the purchase of ARVs in 2016 increased compared to 2015 and amounted to 22,326,790,166 rubles. However, this amount included the amount for the provision of transition period in 2017.
5. At the same time, the nomenclature of procurement in the Russian Federation does not comply with international guidelines against a number of criteria regarding the use of combination forms:
 - a. The nomenclature of procurement does not contain **the combination drug tenofovir/emtricitabine (or lamivudine)/efavirenz once-daily, single-tablet**, which is the preferred regimen according to the WHO 2016 protocols - because the drug was approved in the RF only in July 2016, was not included in the VED List and was physically unavailable on the territory of the country.
 - b. Extremely limited access to combination "complete one-pill regimen" drugs. Despite the fact that the number of patients on such drugs increased about 5-fold, this is, according to monitoring, less than 1% of the total number of patients on treatment. This practice contravenes WHO guidelines and numerous scientific studies showing the benefits of using such regimens.
 - c. The analysis of purchases showed that, unfortunately, the tendency to break down the combination drugs into mono-components continues. Only 38% of the total number of patients received "2-in-1" combination drugs. At the same time,

monitoring data shows that the price reduction due to the dividing of combination drugs into mono-components is not achieved in all cases.

6. The prices of ARVs decreased for the first time in three years of decentralized purchases (an average of 8%). The largest decrease in the price was for the following drugs: tenofovir (85%), abacavir (60%), and nevirapine (54%).
7. The cost of basic treatment regimens also decreased, but almost exclusively due to decreased prices for the above drugs. For example, the weighted average cost of the first-line regimen of tenofovir + lamivudine + efavirenz was 25,000 rubles for the one-year course, and the cost of the second-line regimen tenofovir + lamivudine + atazanavir + ritonavir - 118 thousand rubles for the one-year treatment course.
8. The main share in the budget is occupied by five drugs, for four of which there are no analogues in the Russian market due to the effective patent (lopinavir/ritonavir, atazanavir, raltegravir, etravirine). Raltegravir consistently takes 10% in the budget, with less than 3% of patients receiving it (about 6 thousand).

RECOMMENDATIONS

1. According to the analysis, approximately 235,000 people received ARV therapy in RF in 2016; respectively, in order to cover a larger number of patients, a significant increase in the budget for the purchase of drugs at both the federal and regional levels is required. The allocation/increase of regional budgets will allow to reduce the risks of possible disruptions in the provision of therapy, as well as to purchase drugs not included in the VED List for patients who need them as clinically indicated.
2. Under conditions of a limited budget, an urgent and significant decrease in the prices for a number of drugs is necessary, mainly for lopinavir/ritonavir, tenofovir/emtricitabine, atazanavir, raltegravir, etravirine, and darunavir. To reduce prices, the following mechanisms might be used:
 - a. To cover the need for therapy, it is recommended that a compulsory license be issued for at least three drugs under patent protection in order to achieve a meaningful budget reduction: lopinavir/ritonavir and raltegravir, as drugs that occupy a large share in the budget and will remain under patent protection for a long time, and tenofovir/emtricitabine as a drug that should be more widely used in clinical practice. The possibility of issuing a compulsory license in the event of a security threat to the Russian Federation is provided for in articles 1360 and 1362 of the Civil Code of the Russian Federation.
 - b. The possibility of introducing a set of additional measures to reduce the prices of ARV drugs should be considered, namely direct negotiations with manufacturers, taking into account the planned volumes of purchases and long-term contracts with manufacturers, with possible revision of the prices for drugs if they decrease by more than 30% in reference countries. Pediatric forms might be used as a pilot project for the implementation of long-term contracts.
 - c. For centralized procurement, prices for drugs in contracts should be fixed at the minimum level that will allow to provide the required number of patients with ARV therapy.
 - d. For procurement within the regional budgets, healthcare institutions or authorized bodies need to be guided by registered prices but by actual prices (minimum, average prices, prices of centralized procurement). The Ministry of Health of the Russian Federation should conduct work to inform the regions about the prices that they managed to achieve in the process of centralized bidding.
3. The analysis of purchases showed that measures to optimize the nomenclature of ARV drugs are needed. So, for example, it is necessary to significantly expand access to treatment options recommended in international standards, and to abandon obsolete highly toxic drugs. Among other things, it is necessary to:

- a. Add to VED List and, if necessary, to other applicable lists, the following drugs: tenofovir/emtricitabine, tenofovir/emtricitabine/efavirenz, rilpivirine, dolutegravir, emtricitabine, raltegravir chewable tablets, maraviroc.
 - b. Take measures to exclude stavudine, indinavir and nelfinavir from the VED List.
- 4. The report data show a discrepancy between the number of purchased courses and the stated number of patients on therapy. According to the authors of the report, the main reason for this discrepancy is the problem of patients discontinuing therapy. That is, there is a need for intensive work on the formation of adherence to ARV therapy in patients (strict adherence to the prescribed regimen). According to the recommendations of the World Health Organization, in addition to optimizing the nomenclature of procurement, measures to promote adherence might include:
 - a. Low threshold programs for vulnerable groups to keep them in treatment programs;
 - b. Introduction of multidisciplinary teams in AIDS centers.