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- IX НАЦИОНАЛЬНЫЙ КОНГРЕСС С МЕЖДУНАРОДНЫМ УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ И ФАРМАКОЭПИДЕМИОЛОГИИ В РОССИЙСКОЙ ФЕДЕРАЦИИ» – «ФАРМАКОЭКОНОМИКА – 2015» 16-17 марта 2015 г., УФА, AZIMUT ОТЕЛЬ УФА

PHARMACOECONOMIC ANALYSIS OF EVIPLERA (RILPIVIRINE/TENOFOVIR/EMTRICITABINE) IN THE TREATMENT OF HIV/AIDS IN THE RUSSIAN FEDERATION

Kulikov A. Yu., Babiy V. V.

Department of organization of medical provision and pharmacoeconomics, I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation

Abstract: The aim of this study was to determine the optimal medical technique of treatment of human immunodeficiency virus (HIV) infected adults with HIV-1 RNA < 100 000 copies/ml by assessing costs and effectiveness of highly active antiretroviral therapy: rilpivirine/ tenofovir/ emtricitabine (single tablet regimen (STR)), efavirenz + tenofovir/ emtricitabine (multi-pill regimen), lopinavir + tenofovir/ emtricitabine (multi-pill regimen). The obtained results have demonstrated that prescription of rilpivirine-containing combined Highly Active Antiretroviral Therapy (HAART) (STR) is associated with additional costs on ambulatory treatment, that are overlaid by lower costs (direct and indirect) on new persons with HIV, infected by the analyzed group. Therefore, cost savings, as compared to mentioned schemes of HAART, accompany prescription of the scheme rilpivirine/ tenofovir/ emtricitabine (Eviplera), according to the «budget impact» analysis.

Key words: human immunodeficiency virus (HIV), highly active antiretroviral therapy (HAART), modeling, cost analysis, effectiveness analysis, budget impact analysis, adherence.

Despite certain success in the control of human immunodeficiency virus (HIV) infection achieved in the recent years, we were not yet able to prevent the spread of HIV infection. Since the start of the global epidemic, UNAIDS (United Nations Program on HIV/AIDS) had registered 78 million cases of HIV infection; about half the patients had died [49].

According to the Global Burden of Disease Study, HIV infection is one of the leading causes of premature death in the population of the Russian Federation [42]. Thus, according to the Federal Scientific and Methodological Center for AIDS Prevention and Control, 864,394 HIV-infected patients were registered in the Russian Federation as of November 1, 2014; since the start of the monitoring in 1987, a total of 171,555 cases of death of HIV-infected persons were registered. Along with that, mortality rate in HIV-infected patients in the Russian Federation has increased by 6.1% during the first ten months of 2014 comparing to a similar time interval of 2013 [19].

Generally, HIV infection is a considerable burden on the world economy. According to UNAIDS estimates, 22-24 billion US dollars were required in 2013 only for the medical care of such patients. Meanwhile, various funds across the world have raised only 19.1 billion US dollars. About 33% of new cases of infection are registered in people aged from 15 to 24 years [30]. The results of a systematic review of various studies at Monash University, Australia, showed that HIV infection had a significant negative influence on countries' economic status. The degree of influence depends on epidemic scale, social and demographic factors and the pattern of HIV infection spread among the working population [39]. Taking ten countries as an example, it was estimated that the indirect economic impact of HIV epidemic spread can be expressed as a 0.3% decrease in GDP per capita [43].

Within the scope of evaluation of social and economic consequences of HIV infection epidemic in Russia conducted by ISP Fund (Fund for Intersectoral Social Partnership Development), the government total losses in 2011 were estimated at 92.3 billion rubles (0.2% of GDP). Besides, the majority of expenditures was due to premature death and increased morbidity in HIV-infected patients.

Introduction of HAART in 1996 led to a decrease in global morbidity and mortality rates. This type of therapy implies concomitant prescription of three or more medicinal products (MP) from different groups of antiviral (anti-HIV) medicines [3]. Use of HAART allows increasing the lifespan in young HIV-infected patients by 10 to 35 years [31, 36]. During the period from 1995 to 2004, the percent of HIV-infected patients surviving from 20 to 40 years increased from 1.2% to 36.4% [13, 51]. Due to introduction of HAART, HIV infection mortality rate during the period from 2005 to 2012 decreased by 30%. Overall, 12.9 million people in 2013 had access to HAART, which is by 5.6 million people more than in 2010 [33].

Current HAART is effective enough for viral suppression, so HAART requirements have also changed in the recent years: besides being effective, antiretroviral MP need to be convenient for use and have a toxicity profile as low as possible.

The results of I.C.O.N.A. study demonstrated that in 862 patients during the first line of therapy, treatment interruption was caused by MP toxicity in almost half the cases and by non-compliance in 20% of the cases [29].

Along with the negative impact on the quality of life, side effects may decrease treatment compliance, which in turn may cause HIV resistance to MP or a combination of drugs (in case of cross-resistance), lead to additional costs for resistance testing and, if a decision will be made to continue therapy, will significantly decrease the efficacy of MP use, requiring selection of new and more costly treatment regimens later on.

Unlike many other diseases, where compliance level of 80% is regarded as "good", adherence to physician's prescriptions in case of HAART should be over 95%.

As patients receiving HAART have to take MP from one to four times a day for several years, treatment compliance is an important matter for any HIV-infected patient.

In order to increase compliance, the development of fixed-dose combinations was started since 2000, which allows reducing the number of tablets taken concomitantly. Today, MP that contain a complete HAART regimen in one tablet are present on the market.

The only product containing a complete HAART regimen in one tablet to be taken once a day in adult patients with HIV infection during first line therapy that is currently registered in the Russian Federation, is a fixed-dose combination of rilpivirine/ tenofovir/ emtricitabine (Eviplera). The use of such



a fixed-dose combination, combining convenience of use of one tablet once a day and a high level of safety, opens up new possibilities for the ART in HIV-infected patients.

Therapy regimen including a fixed-dose combination in one tablet comparing to a regimen with intake of three tablets a day allows increasing treatment compliance by 1.6-fold and decreasing the number of hospitalizations by 21% [46].

Meanwhile, introduction of HAART had led to medical cost increase by 55% and by 23% in the AIDS stage [21]. However, due to the fact that HAART prolongs life and increases working ability of HIV-infected patients, as well as decreases the HIV infection dissemination rate, the use of HAART allows decreasing the total social and economic burden of the disease.

The aim of this study was to determine an optimal medical technique of HIV infection treatment (during first line HAART) in adults with HIV-1 RNA <100,000 copies/ml, by means of pharmacoeconomic analysis and assessment of the costs and effectiveness of the following regimens:

- HAART - single-tablet regimen: rilpivirine/tenofovir/emtricitabine (Eviplera);
- HAART - multi-tablet regimen:
 - o efavirenz + tenofovir /emtricitabine;
 - o lopinavir + tenofovir /emtricitabine.

The chosen comparison regimens are the preferred regimens of first-line ART according to major international and Russian guidelines on treatment of HIV-infected patients:

- National Clinical Recommendations on Diagnostics and Treatment of HIV Infection in Adults. National Virology Association, 2014.
- Protocols of Dispensary Follow-up and Treatment of HIV-infected Patients. National Scientific Society of Infectionists, 2014.
- Guidelines. Version 7.1. European AIDS Clinical Society(EACS), 2014.

Besides, efavirenz- of lopinavir-containing regimens are the most frequently prescribed HAART regimens during first line treatment in Russian medical practice [18].

Population Characteristics

Analyzed population included adult patients with HIV-1 RNA in the range of $\leq 100,000$ copies/ml and CD4+ level = 350-500 mcl^{-1} . Cohort size was 70,453 patients, corresponding to a number of detected HIV-seropositive persons registered in the Russian Federation in 2012 [7]. It was also assumed that HAART will be indicated in all the patients simultaneously due to a decrease in $\text{CD4+} < 500 \text{ mcl}^{-1}$.

HIV-infected patients in the population analyzed represented four age groups from 15 to 54 years of age, corresponding to age groups in the study reflecting relations between the duration of a certain HIV infection stage and mortality and CD4+ lymphocytes level [47]. Data on gender and age distribution in the population were calculated using materials of the Federal Scientific and Methodological Center for AIDS Prevention and Control published in 2013 and materials of the Federal State Statistical Service published in 2014 (year 2012 data was used in both sources). Due to the fact that the age of some patients in the Russian Federation was outside the range of the studied age categories (3% of the total number of HIV-infected patients), this patient group was excluded from further analysis [7]. Characteristics of the population studied are presented in Table 1.

Table 1. Analyzed Population Characteristics

Parameter	Value	Reference
Number of patients	70453	[7]
Male, %	63,7	[7]
Female, %	36,3	[7]
IDU+*, %	56,1	[7]
IDU-**, %	43,9	[7]
Age, %		
15-24	7,9	[7]
25-34	57,1	[7]
35-44	26,1	[7]
45-54	6,1	[7]

* IDU+ - injection drug users.

** IDU- - not injection drug users.

Efficacy Analysis

Efficacy assessment in the current work was based on modeling of the HAART regimens stated above during first line therapy in a group of HIV-infected patients with HIV-1 RNA values $\leq 100,000$ copies/ml and CD4+ level = 350-500 mcl^{-1} . For the calculations needed, a combined mathematical model was created in Microsoft Office Excel 2013, which included two submodels:

- o Analytical submodel ("decision tree") (Fig. 1);
- o Simulation Markov submodel (Fig. 2).

The first submodel allows estimating the number of patients in the analyzed cohort reaching the target clinical endpoint: complete suppression of viral replication, i.e. HIV RNA level decrease to undetectable levels (less than 50 copies per ml). At the first branching, part of the analyzed cohort switches to alternative therapy regimens due to virologic failure and severe adverse drug reactions (ADR). At further branching, depending on therapy compliance level, the corresponding parts of the analyzed cohort are divided into patients, who achieved the clinical endpoint indicated above and those who did not.

Data on the effect of compliance level depending on therapy regimen (single-tablet of multiple-tablet HAART) on therapy efficacy are based on the studies by Antinori A. [24] and Bangsberg D. [26]. The Results of these studies have shown that using a therapy regimen with one tablet a day is associated with a higher level of compliance and a higher level of efficacy. Besides, the mentioned papers have shown that the group of homeless/fringe patients had a therapy compliance level significantly lower compared to the total group.

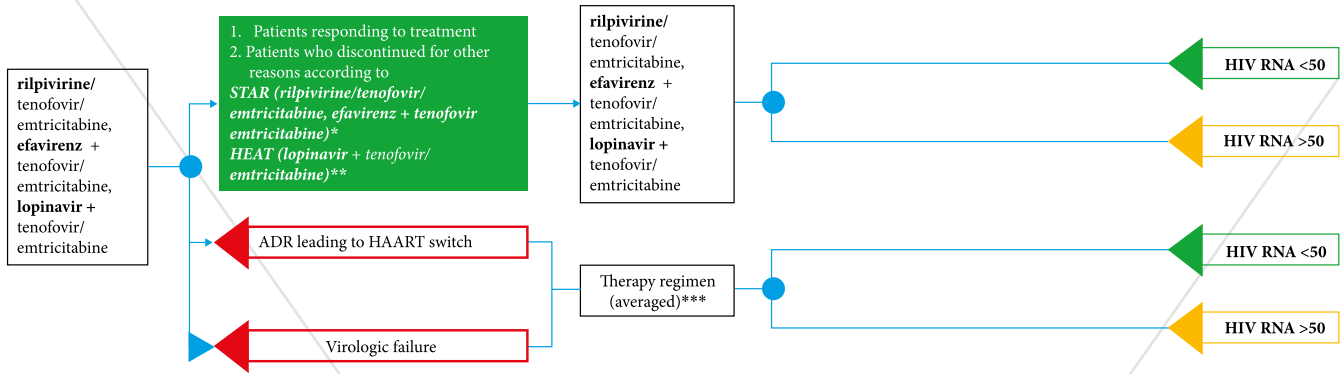
In order to account for the difference in therapy compliance in various social groups, we used the materials of O.S. Levina study "Assessment of Social and Psychological Characteristics of Attitude to HAART in HIV infected Patients of "Hidden Groups" Localized in General Population, In Most Cases in Fringe Groups" in Saint Petersburg and Orenburg (injection drug users (IDU), women employed in commercial sex industry, hospitalized patients and members of self-assistance groups). According to this study, more than 75% of the studied group representatives had a complete or incomplete secondary, vocational secondary or vocational education [11]. Taking into account the results of the survey conducted during the study led by prof. N.B. Dremova in Kursk, Belgorod and Voronezh HIV/AIDS centers, showing that 70.5% of responders had incomplete secondary or vocational secondary education and 73.5% of the total number of responders had low income (up to one subsistence minimum wage per one member of household) [8], modeling in the current study also considered the social status influence (fringe or general group representative) on the level of therapy compliance.

The second submodel was developed to simulate HIV infection progression and patient's death during a five-year period (one cycle duration is 1 year) depending on reaching the stated clinical endpoint, CD4+ lymphocyte level, age and gender. The stated modeling horizon was chosen based on expert opinion on mean duration of first line HAART for a patient in Russia in case it is effective (HIV RNA level <50 copies/ml).

As we could not find any results of studies conducted in the Russian Federation in a population of HIV-infected patients, that would include the data needed for the development of the simulation model (probability of disease progression, probability of death in HIV-infected patients receiving or not receiving HAART), the data in the current work were obtained from the studies conducted in Eastern Europe by leDEA (The International Epidemiologic Databases to Evaluate AIDS) as part of the AIM (AIDS Impact Model) project [47]. Considering that HAART efficacy (in the absence of severe ADR and virological failure) is determined by therapy compliance, it was assumed that the probability of infection progression and/or death in patients with viral load above detection level would be similar to probabilities estimated for patients not receiving HAART. If viral load is below detection level, the corresponding probabilities are assumed to be equal to those in patients receiving HAART. It is important to emphasize that no disease progression was assumed if HIV RNA decreased below detection limit.

Besides, the model contains a module which allows calculating the number of new HIV-infected persons due to sexual contact and/or injection drugs use with the analyzed cohort representatives during five years. Analysis of HIV transmission during shared drug use was performed considering an extremely high level of drug use among HIV-infected patients [7]. Most of the necessary data regarding the characteristics of HIV-infected population (the number of sexual contacts among males (M+F, M+M) and females (M+F) in groups of injection drug users (IDU+) and non-users (IDU-); number of contacts using condom in IDU+/IDU-; number of shared injections in IDU+ group) and the probability of viral transmission by the above mentioned routes were taken from the studies conducted in the Russian Federation and Eastern European countries [23, 45].

Figure 1. "Decision tree" Model (common for all analyzed therapy regimens)



* - Cohen C, et al., 2013.

** - Smith K. et al., 2009.

* - Standard of Primary Medical Care in Disease Caused by Human Immunodeficiency Virus (HIV-infection) dated Dec. 24, 2012.

Figure 2. Markov Model of the base for the Efficacy analysis

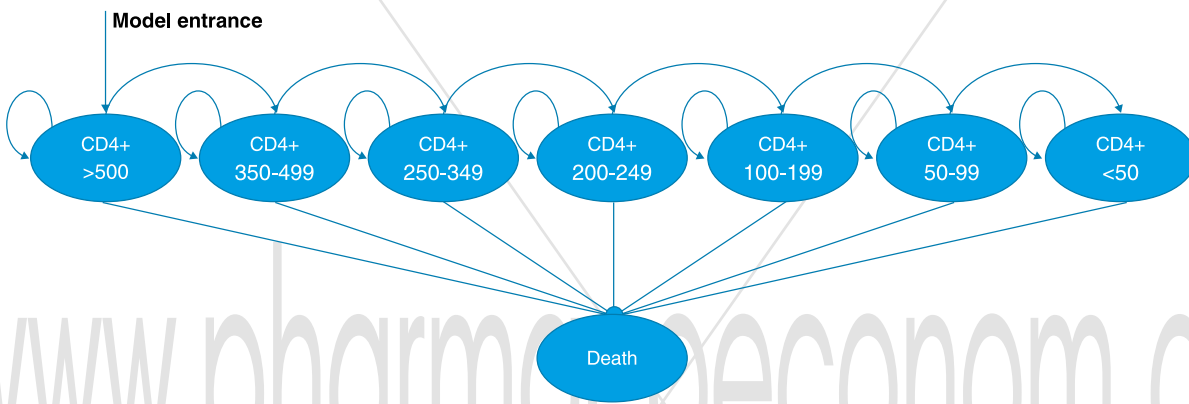


Figure 3. Analysis of cases of HIV transmission by patients due to sexual contacts during five years

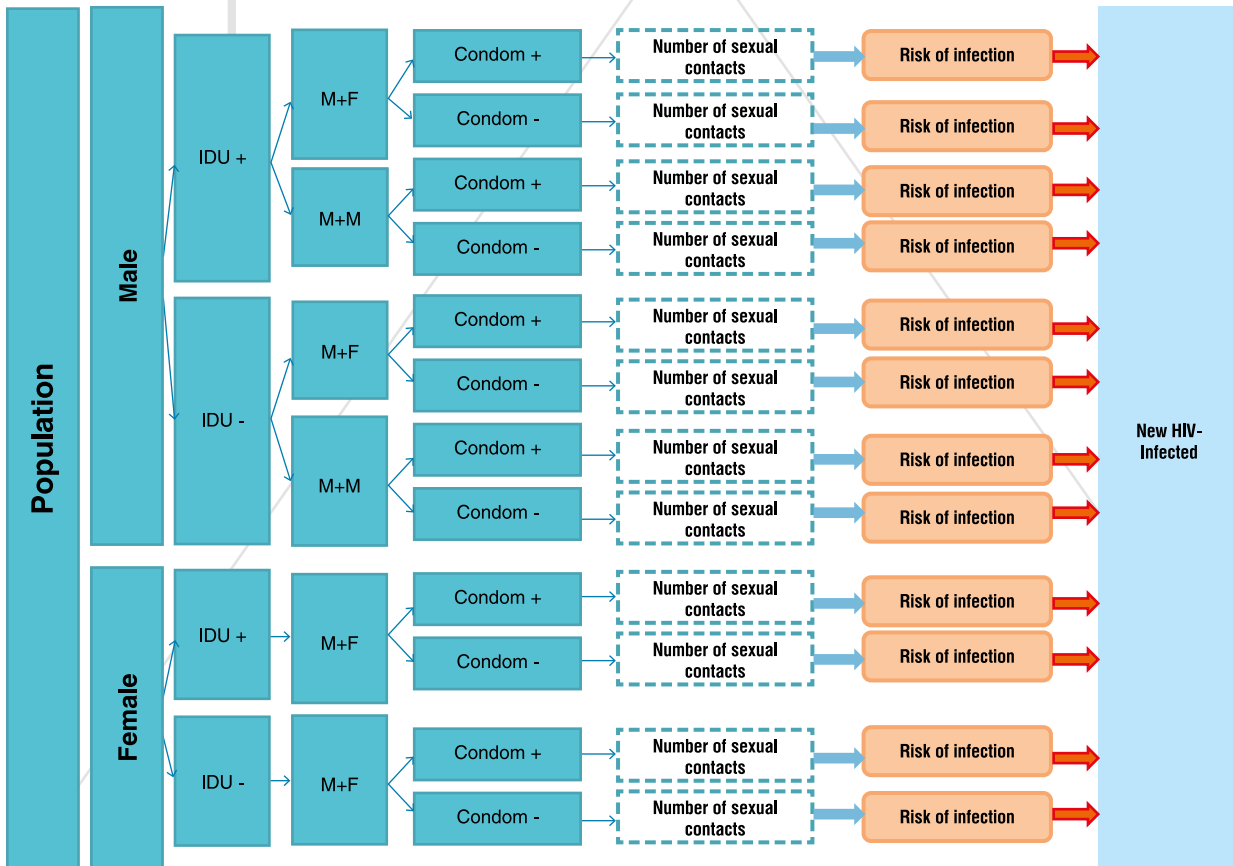




Figure 3 shows the scheme of HIV transmission during sexual contact used in the current study. Probability of virus transmission during sexual contact depended on:

- using or not using injection drugs (IDU-/IDU+);
- the number of sexual contacts;
- the character of sexual contacts;
 - o males having sexual contacts with males;
 - o males having sexual contacts with females;
- not using/using a condom.

It should be noted that injection drug users had more sexual partners comparing to people not using injection drugs.

Modeling accounted for HAART influence on HIV transmission both during sexual contact and shared drug use. If target levels of HIV RNA <50 copies/ml were achieved, the probability of transmission decreased [27, 44, 37].

Cost Analysis

Cost analysis included direct and indirect costs due to therapy of HIV-infected patients using regimens analyzed (Fig. 4). Cost data were obtained from Compulsory Medical Insurance Fund tariffs, standards of inpatient and outpatient medical care, health institution price lists, data of MP wholesale purchase (IMS), State Register of Higher Limits of Consumer Prices and pharmindex.ru portal.

Price data for the MP analyzed were obtained from the State Register of Higher Limits of Consumer Prices (including VAT) or, in case the duly registered higher price limit for MP was absent, by analyzing the mean tender prices of Q4 2014 (source: IMS). Eviplera (rilpivirine/ tenofovir/ emtricitabine) price was taken as a price planned for registration as the highest consumer price (including VAT).

Table 2. Prices data for MP included in the HAART regimens analyzed

Medicine	Unit price	Reference
<i>Eviplera</i> (rilpivirine/ tenofovir/ emtricitabine)	25 300 ₺	High limit of consumer price planned for registration (including VAT).
<i>Lopinavir + ritonavir</i>	8 039 ₺	State Register of Higher Limits of Consumer Prices (including VAT)
<i>Efavirenz</i>	803 ₺	State Register of Higher Limits of Consumer Prices (including VAT)
<i>Tenofovir/ emtricitabine</i>	10 691 ₺	IMS: MAT/2014/MTH12/QRT4

Direct cost calculations in the current study were based on the standards (Table 3, 4):

- Standard of Primary Medical Care in Disease Caused by HIV-infection dated Dec. 24, 2012 [17];
- Standard of Specialized Medical Care in Disease Caused by HIV-infection dated Nov. 09, 2012 [16];

If therapy regimen remained unchanged, calculation of outpatient therapy cost was based on "the Standard of Primary Medical Care in Disease Caused

by HIV-infection" with HAART defined by the standard changed for one of the analyzed therapy regimens. In cases of switch from the primary scheme, the mentioned standard was used unchanged (excluding the guideline on resistance testing frequency, which was changed to 1).

Indirect costs due to premature death of a patient were calculated based on the current data on mean life expectancy in HIV-infected patients. According to these data, life expectancy at birth is 13 years lower in HIV-infected persons [23] and 23 years lower in HIV-infected injection drug users [1] comparing to mean life expectancy in people without HIV infection.

Besides, the analysis included the costs related to HIV infection transmission, such as the costs of outpatient care in new HIV-infected patients during expected life span and costs as GDP loss due to premature death of a HIV-infected patient.

Results

A result of modeling for HAART during five years, the majority (68%) of patients reached HIV RNA <50 copies/ml using rilpivirine/ tenofovir/ emtricitabine (Eviplera) regimen (including patients using this regimen as well as patients switched to an averaged regimen). Besides, prescribing the given therapy regimen was associated with the increased number of hospitalizations comparing to lopinavir + tenofovir / emtricitabine and efavirenz + tenofovir / emtricitabine regimens: by 24.86% and 24.81%, respectively

It should be noted that according to the obtained results, mortality was also lower in the group initially receiving rilpivirin-containing regimen. Number of life years lost with the use of this regimen was by 9% and 12% lower comparing to regimens including lopinavir and efavirenz, respectively. Number of life years gained (LYG) with this regimen was maximal - 4.866 years. Taking into account that level of HIV control affects patient's quality of life, the value of Quality adjusted life years (QALY) was also maximal with the rilpivirin / tenofovir / emtricitabine regimen (QALY = 3.819).

Despite the lower levels of mortality during five years in patients using rilpivirin / tenofovir/ emtricitabine regimen, the use of this regimen was also associated with the lower number of new HIV cases. Comparing to regimens including lopinavir and efavirenz, the difference was 13% (9570 cases) and 10% (7262), respectively.

Results of the efficacy assessment of the studied therapy regimens with discounting are presented in Table 3.

Analysis of medical care costs in HIV-infected patients in outpatient and inpatient settings showed that the main costs are due to medication therapy (Table 4, Table 5). Overall, the total costs of outpatient medical care in HIV-infected patients are higher than the costs of inpatient medical care. At that, the yearly HAART costs are the lowest for efavirenz + tenofovir/ emtricitabine regimen. However, due to the lower number of hospitalizations, the total costs of hospitalization are lower with rilpivirin-containing regimen.

Taking into account that prescribing rilpivirin-containing regimen in the analyzed cohort led to a smaller number of new HIV-infected patients, the costs of outpatient medical care in the latter during expected lifespan are also lower (by 13% and 16% comparing to lopinavir- and efavirenz-containing regimens, respectively).

Figure 4. Cost structure included in the current study.

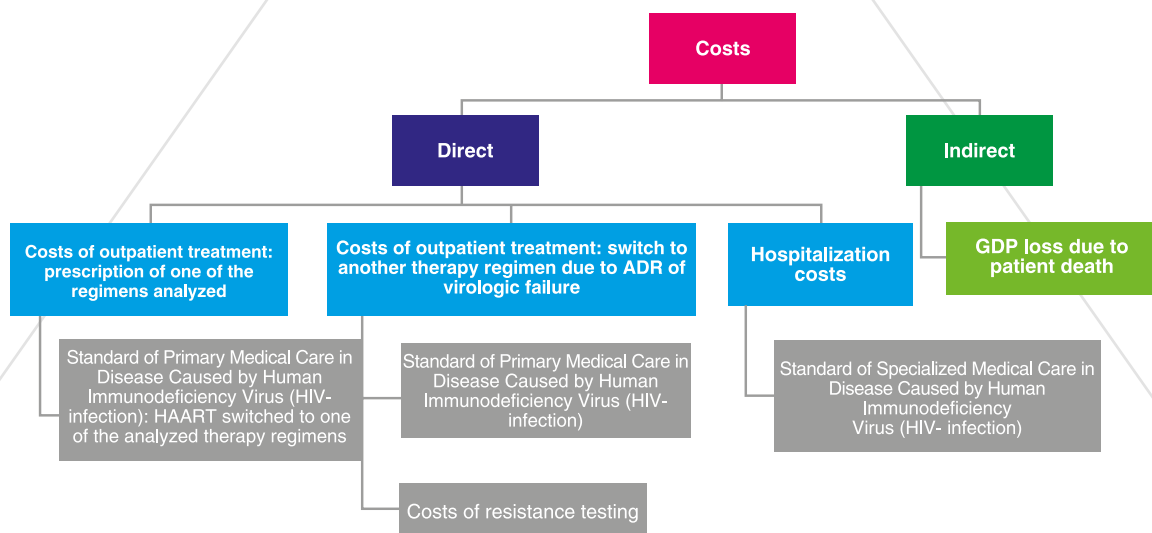


Table 3. Results of the efficacy analysis of the studied therapy regimens during five years

	Rilpivirine/ tenofovir/ emtricitabine (Eviplera)	Lopinavir + tenofovir / emtricitabine	Efavirenz + tenofovir / emtricitabine	Discounting (3%)
Number of new patients with HIV infection, n	49933	57196	59504	-
	44206	50635	52678	+
Number of life years lost (for 1 averaged patient from the primary population), years	0,51	0,56	0,58	-
	0,45	0,50	0,51	+
Percentage of patients with RNA<50 copies/ml (of the number of patients with MP initially prescribed), %	68	49	47	-
	60	44	41	+
Number of hospitalizations (for 1 averaged patient)	1,951	2,436	2,435	-
	1,727	2,156	2,156	+
LYG (Life years gained)	4,866	4,860	4,858	-
	4,308	4,302	4,301	+
QALY (Quality adjusted life years)	3,819	3,807	3,803	-
	3,381	3,371	3,367	+

Table 4. The results of direct medical costs analysis per one HIV-infected patient in outpatient settings during 365 days

Medical service name	Medical care cost, rubles			
	Rilpivirine/ tenofovir/ emtricitabine (Eviplera)	Lopinavir + tenofovir / emtricitabine	Efavirenz + tenofovir / emtricitabine	Y Averaged therapy regimen*
Medical procedures for diagnostics of a disease or condition	9 329	9 329	9 329	9 329
Visit (physical examination, consultation) by a specialized physician	1 049	1 049	1 049	1 049
Laboratory investigation methods	7 171	7 171	7 171	7 171
Instrumental investigation methods	1 109	1 109	1 109	1 109
Medical services for disease or condition treatment and treatment control	13 670	13 670	13 670	24 470
Visit (physical examination, consultation) and follow-up by a specialized physician	1 272	1 272	1 272	1 272
Patient follow-up and care by a medical professional with secondary (primary) professional education	26	26	26	26
Laboratory investigation methods	11 168	11 168	11 168	21 968
Instrumental investigation methods	1 162	1 162	1 162	1 162
Surgical, endoscopy, endovascular and other treatment modalities requiring anesthesia and/or resuscitation support	1	1	1	1
Non-pharmacological methods of prophylaxis, treatment and medical rehabilitation	40	40	40	40
List of pharmaceutical products for medical use registered in the Russian Federation, with mean daily and course doses	317 221	188 381	149 246	183 404
TOTAL:	340 220	211 380	172 245	217 203

*The costs were calculated based on averaged therapy regimen, presented in the Standard of Primary Medical Care in Disease Caused by HIV-infection [17].



Table 5. The results of direct medical costs analysis per one HIV-infected patient in inpatient settings during 30 days

Medical service description	Medical care cost, rubles
Medical procedures for diagnostics of a disease or condition	7 692
Visit (physical examination, consultation) by a specialized physician	707
Laboratory investigation methods	4687
Instrumental investigation methods	2299
Medical services for disease or condition treatment and treatment control	7 438
Visit (physical examination, consultation) and follow-up by a specialized physician	3945
Laboratory investigation methods	2818
Instrumental investigation methods	22
Surgical, endoscopy, endovascular and other treatment modalities requiring anesthesia and/or resuscitation support	454
Non-pharmacological methods of prophylaxis, treatment and medical rehabilitation	200
List of pharmaceutical products for medical use registered in the Russian Federation, with mean daily and course doses	63 843
Inpatient hospitalization	12 550
Types of clinical nutrition, including specialized food for clinical diet	9 238
TOTAL:	100 761

Summarizing direct medical costs in the analyzed cohort for five years and outpatient medical care costs in new HIV-infected patients during expected lifespan, it was estimated that rilpivirine-containing regimen was associated with lower costs comparing to the schemes including lopinavir (by 654,683,660) and efavirenz (by 842,868,590).

Minimal GDP loss due to premature death of a patient was observed after prescribing rilpivirine/ tenofovir/ emtricitabine (Eviplera). Besides, prescribing Eviplera regimen in the analyzed cohort caused a decrease in GDP loss due to premature patients deaths (in new HIV-infected persons) that compensated

for the necessary additional outpatient medical care costs in the analyzed cohort during five years comparing to the other HAART schemes.

Overall, the total costs (direct or indirect costs in the analyzed cohort and in the group of new HIV-infected persons) were the lowest with the ART regimen using Eviplera (Fig. 5).

"Budget impact" analysis has shown that switching from multi-tablet efavirenz- and lopinavir-containing schemes to a single tablet rilpivirine-containing regimen may lead to a total cost decrease by 46 billion and 62 billion rubles (Fig. 6).

Figure 5. Results of cost analysis of prescribing analyzed HAART regimens (for five years)

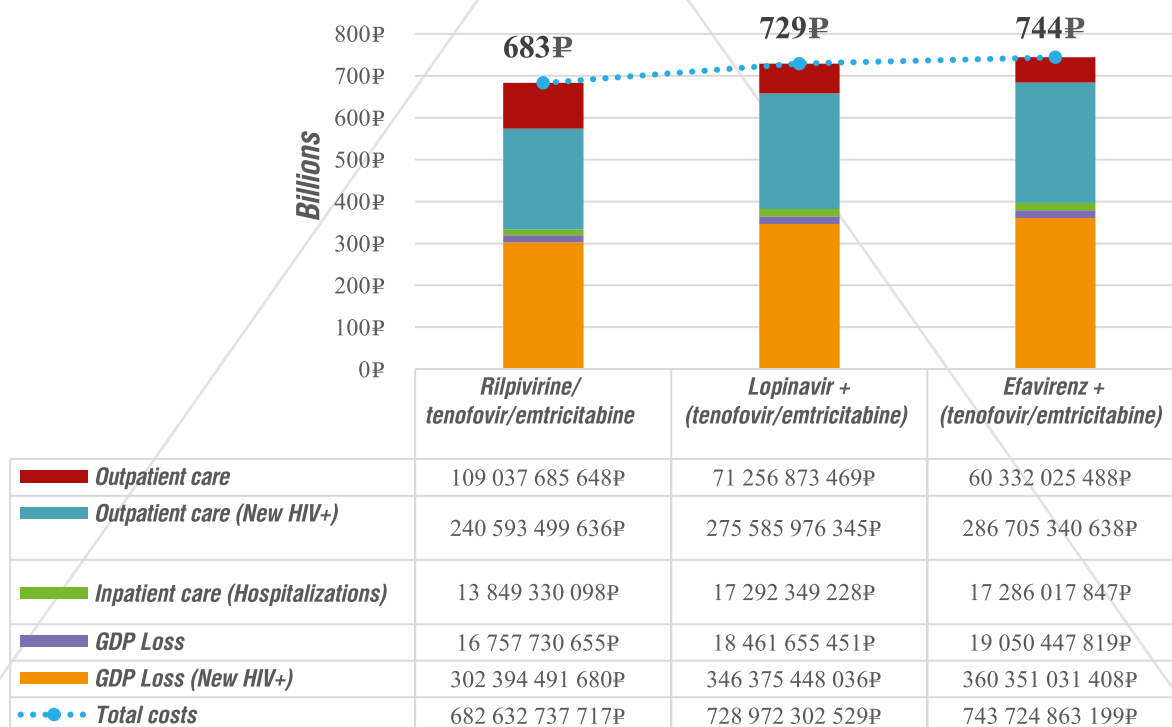
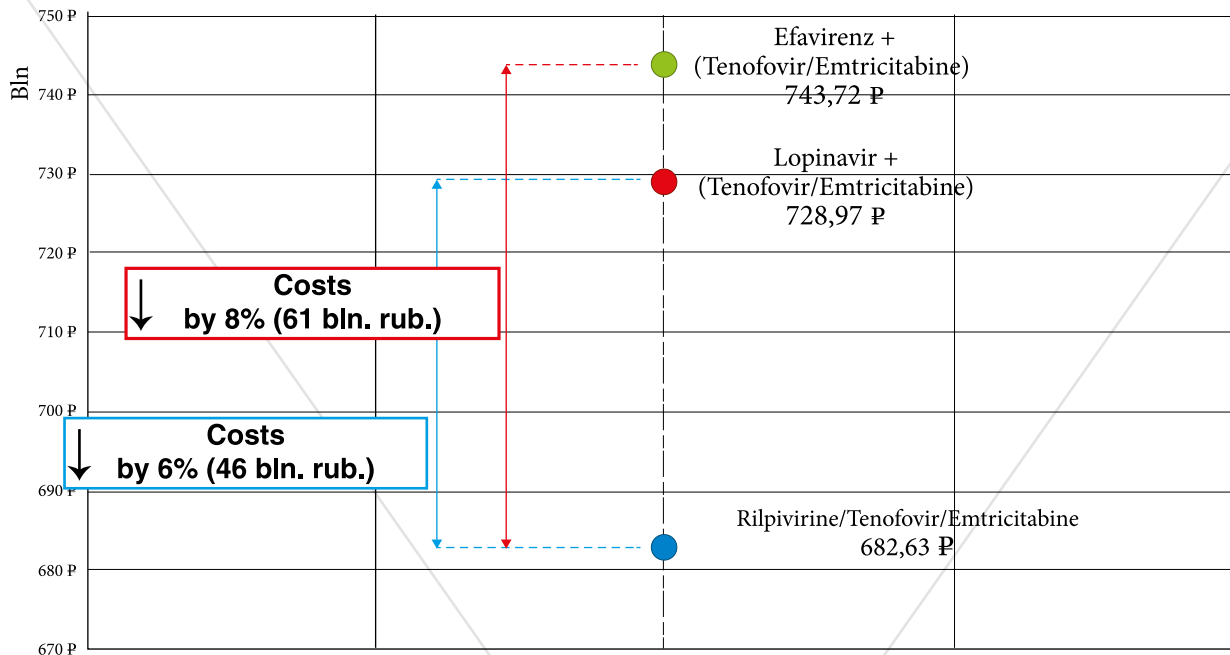


Figure 6. Results of "budget impact" analysis when prescribing rilpivirine/ tenofovir/ emtricitabine instead of alternative therapy regimens (for five years)



Conclusions

The current analysis has determined that using a single tablet HAART regimen (Eviplera) allows a better HIV control comparing to regimens that require several tablets intake.

Despite higher overall HAART costs using rilpivirin-containing regimen, this ART allows better HIV control and allows decreasing the number of patient hospitalizations, the number of new cases of HIV infection and mortality in the group of HIV-positive patients. Besides, using this regimen is associated with the lower working population loss and, thus, with the lower GDP loss. It should be noted that the assessment of therapy regimens analyzed has shown that the higher costs of outpatient therapy (HAART) with rilpivirine/ tenofovir/ emtricitabine regimen are compensated by the lower costs (direct and indirect) for new HIV patients infected by the representatives of the analyzed cohort s.

Thus, rilpivirine/ tenofovir/ emtricitabine (Eviplera) regimen, if used as a first line therapy in adult patients with HIV-1 RNA in the range of $\leq 100,000$ copies/ml is the most optimal and allows reducing the total costs by 46 billion rubles and 61 billion rubles comparing to lopinavir + tenofovir/ emtricitabine and efavirenz + tenofovir/ emtricitabine, respectively.

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