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VALIDATION OF THE "BUDGET IMPACT ANALYSIS" MODEL OF THE INTRODUCTION OF DOLUTEGRAVIR DRUG INTO THE PUBLIC PROCUREMENT OF ANTIRETROVIRAL DRUGS IN THE RUSSIAN FEDERATION

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Summary: *The article demonstrates validation results of the "budget impact" model of introduction of the drug dolutegravir into the public procurement of antiretroviral drugs on the territory of the Russian Federation provided by ViiV Healthcare.*

Keywords: *Human immunodeficiency virus (HIV), antiretroviral therapy (ART), modelling, validation, "budget impact analysis", dolutegravir.*

The purpose of this work was to validate the pharmacoeconomic model provided by ViiV Healthcare to enforce "budget impact analysis" of the introduction of the drug dolutegravir into the public procurement of antiretroviral drugs on the territory of the Russian Federation.

Model description

The pharmacoeconomic model that was presented for analysis, was made in Microsoft Office Excel.

The model was prepared to search for possible ways and financial implications of the introduction of drug dolutegravir into government procurement. The "budget impact analysis" was applied in the model. The horizon of modelling was 5 years (2018-2022).

The model considered the purchase of drugs, which are the third-party components of ART or complex drugs, which contain a complete scheme in one pill and should to be taken once per day: integrase inhibitors (II)-raltegravir, dolutegravir, protease inhibitors (PI)-darunavir, fosamprenavir, saquinavir, atazanavir, lopinavir/ritonavir, nonnucleoside reverse-transcriptase inhibitors (NNRTIs)- etravirine, nevirapine, efavirenz, and combined antiretroviral drug (ARD) rilpivirin/tenofovir/emtricitabine.

The modelled group of patients was the adult patients who had access to ART, regardless of therapy and previous treatment experience.

Only the direct cost of purchasing ARD were considered in the modelling

The sources of the data were the materials of the Kursor auction base, the State Register of Drugs (GRLS), the Unified Information System in the procurement field, and the target indicators of the Government's strategy of countering the spread of HIV infection [2, 4, 6].

The following assumptions were used in this model:

- Comparable efficiency and security of the ART schemes containing the drugs, mentioned above;
- Expansion of dolutegravir procurement;
- Lowering the price of drug in the predicted period by the emergence of generics;
- The adherence to ART at the level of at least 95%.

Evaluation of used methodic

The Microsoft Office Excel software that was selected for the model is a widely used environment for conducting pharmacoeconomic analysis because it does not require many specialized (primarily programming) knowledges, skills and abilities from the end-user (the decision maker), thereby ensuring the necessary level of transparency of the formula apparatus and the ease of change, if necessary.

Based on the fact, that the model considers the costs of ARD, it can according to the classification, be attributed to models analyzing the budget as a separate drug provision program that allows analyzing the budget of the drug provision program for HIV-infected persons. However, because modern ART involves at least three ARDs (the standard ART scheme includes 2 NRTI and the third drug, which may be NNRTIs, boosted or not boosted PI, II), and the proposed drug dolutegravir is II (i.e. as the third component of ART), the model considers the drug provision budget for the treatment of HIV-infected people by third components. The approach may be considered acceptable, with a holistic view of the program being preferable, since the money is allocated to the whole ART without being broken down into subprograms. A separate review of the costs of the basic and third components could lead to the inability to consider a number of dependencies. For example, dependent consumption where there is a connection between the purchase of individual third-party and basic ART components or a situation with the exit of a generic basic ARD can release additional money that could be spent on the purchase of third-party components. However, a preliminary analysis of all the ART components used to treat adult HIV patients in 2014-2017 has shown that nearly all INN in NNRTI group have been replaced by generics, and the ratio of budgets spent to groups of third components and NNRTI remains virtually unchanged: 80%/20%.

This model compares two options for the situation budgeting:

- Option 1: Without the inclusion of dolutegravir in procurement;
- Option 2: Dolutegravir is included in procurement.

First, the budgets for each of the identified developmental variations are calculated on the time line of 2018-2022. It then calculates the difference, determines the possible cost-cutting, and calculates the number of patients that can be additionally cured with the use of released funds (lost opportunity analysis).

Analysis of the calculations structure made it possible to visualize the relationship of the data used in the model in graphic form (Figure 1).

The model takes into account key factors necessary for the analysis of the HIV budget drug supply: the number of patients, the distribution of patients relative to ARD, the average rate of ARD and the price of ARD regimes. The reduction in the price of ARD in connection with the appearance of generic ARDs is also taken into account.

Data on the adherence of HIV-positive patients to treatment were used in calculating the number of ARD procured. Unlike many other diseases, where a level of adherence of 80% is considered to be a "good" indicator, in the case of HAART, compliance with the requirements of a doctor should be at more than 95% [3]. For example, when a patient receives drugs 2 times per day during one month, a patient can skip no more than 3 one-time doses of

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drugs. In general, the compliance requires the patient to do the following: timely drug administration, compliance with doses of drugs and compliance with diet recommendations. Due to the fact that patients who receive ART have to use drug from one to four times a day for many years, adherence to treatment is a matter of urgency for every HIV patient. The tolerance of ARD is an important factor influencing the adherence. The model assumes that the level of adherence is 95%, which is within the necessary framework for effective treatment and avoids a shortage of ARD if the patient's adherence to treatment is increased.

A number of stress tests were conducted in order to verify the correctness of the calculations in the model:

- entering equal values for the patient disposition relative to ARD;
- input of equal prices for ARD;
- the introduction of equal indicators of adherence;
- the change the specified dolutegravir share values within +/-10%;
- the change in the monthly rate of dolutegravir within +/-10%;
- the change in projected price reduction due to generics commercial distribution within +/-10%;
- the change in the number of sick people receiving ART within +/-10%;
- the change in projected reduction of the price due to dolutegravir market exit within +/-10%;
- the change of the specified therapeutic adherence values within +/-10%.

The results obtained after these changes did not reveal structural errors. With the increase in the adherence to therapy, the projected price reduction, the market exit of dolutegravir and the specified values of therapeutic adherence have resulted as an increase in total cost savings. In the case of an increase in projected price reduction, due to commercial distribution of generics, the cost of the monthly dolutegravir and the share of dolutegravir (at the current share of other ARD), the total cost savings were reduced (Figure 2).

Estimation of the used data

The following indicators are required for the model to work: number of patients receiving ART, the patient allocation relative to ARD, the cost of the monthly ARD course, the prognosis of the change in the allocation of the patients relative to ARD, the adherence to therapy, the prediction of the cost of the monthly ARD course in connection with the appearence of generics, the forecast of the change in the monthly rate of the ARD in connection with the appearence of dolutegravir and the average cost of therapy.

The annual number of patients receiving ART was obtained through the analysis of annual sets of therapies based on real purchases and inquiry of Federal Budget Institution Central Scientific Research Institute of Epidemiology of Rospotrebnadzor of December 2016. The distribution of patients relative to ARD in the base and forecast periods was based on the results of real procurement from the Cursor database and trends for the major third-party components identified during the period 2013-2017.

The cost of the ARD monthly course was calculated on the basis of the results of the procurement made in the baseline period 2014-2017 (for all specified ARD except: dolutegravir). The average market value of the dolutegravir monthly rate, including VAT adherence, was calculated from the price proposed by the manufacturer for registration as a maximum sale price. Despite the fact that a number of ARD have a registered maximum sale price, the approach of the authors reflects the real situation on the market more accurately.

The forecast of the change in the monthly rate of ARD in connection with the exit of generic was based on a change in the maximum sale price of darunavir. The model considers the predicted appearance of generics atazanavir and Lopinavir/ritonavir in 2018, and fosamprenavir in 2021. According to Russian law, drug procurement should be carried out in accordance with INN, so it is difficult to analyze changes in the real purchase price after the replaying of INN, but it is preferable. The methodology used in the model can reasonably reflect the possible price change.

The level of adherence used ARD in line with WHO recommendations [8, 10, 12].

Conclusions

Provided by ViiV Healthcare for validation pharmacoeconomic model demonstrated the possibility of including a drug dolutegravir in the public procurement of antiretroviral drugs on the territory of the Russian Federation without the need to increase the size of the budget. In addition, according to the results of the model, the introduction of the dolutegravir will reduce the cost of medication (per capita), which will allow to provide more HIV-infected persons with ART within the same budget level.

Based on the validation of the modelling methodology used and the used data, we found that the approach used in the model was valid and allowed to receive valid results.

In addition, the validation results allowed the formation of a number of recommendations to further improving of the model: take into account the direct medical costs associated with the treatment of HIV infection, the complications of HIV infection and the adverse side effects that appear during the

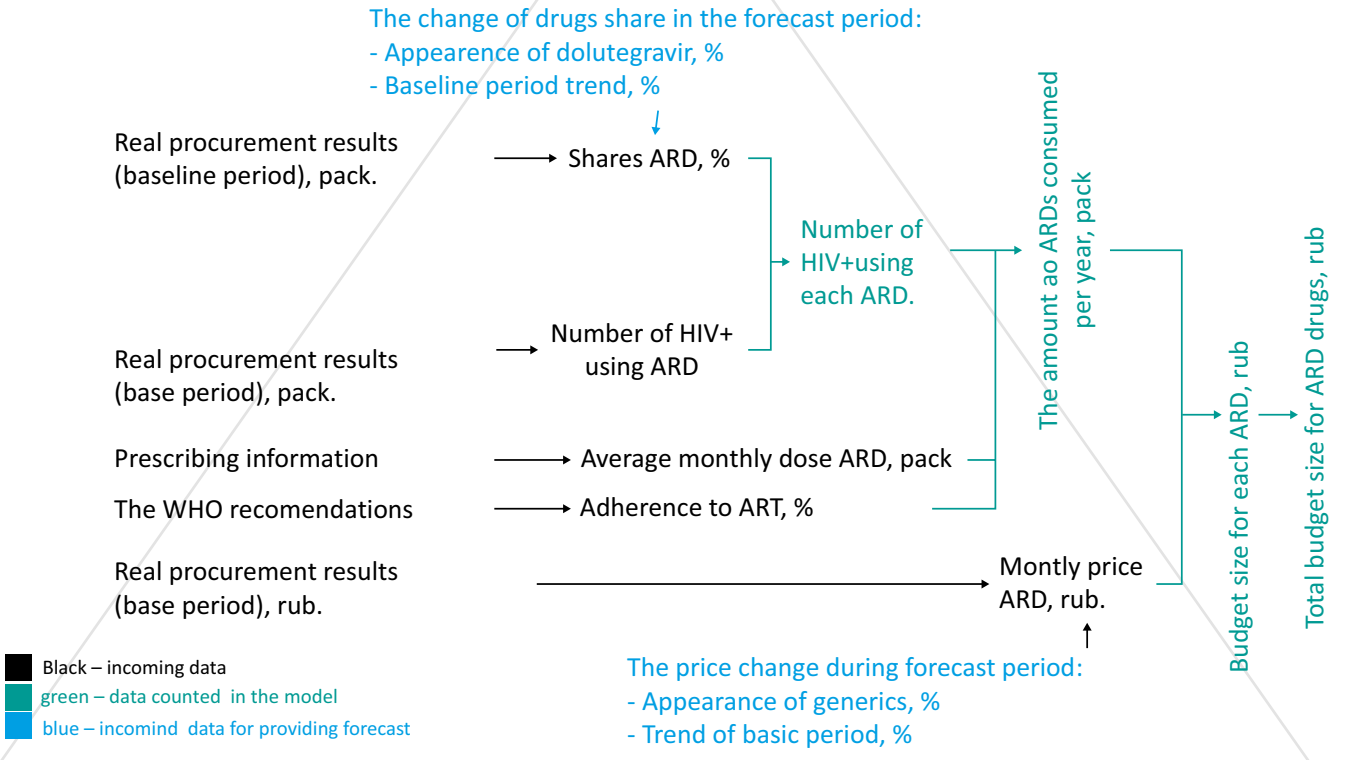

Figure 1. The result of estimating the "budget impact analysis" model structure is: graphical representation of the mathematical apparatus of the model

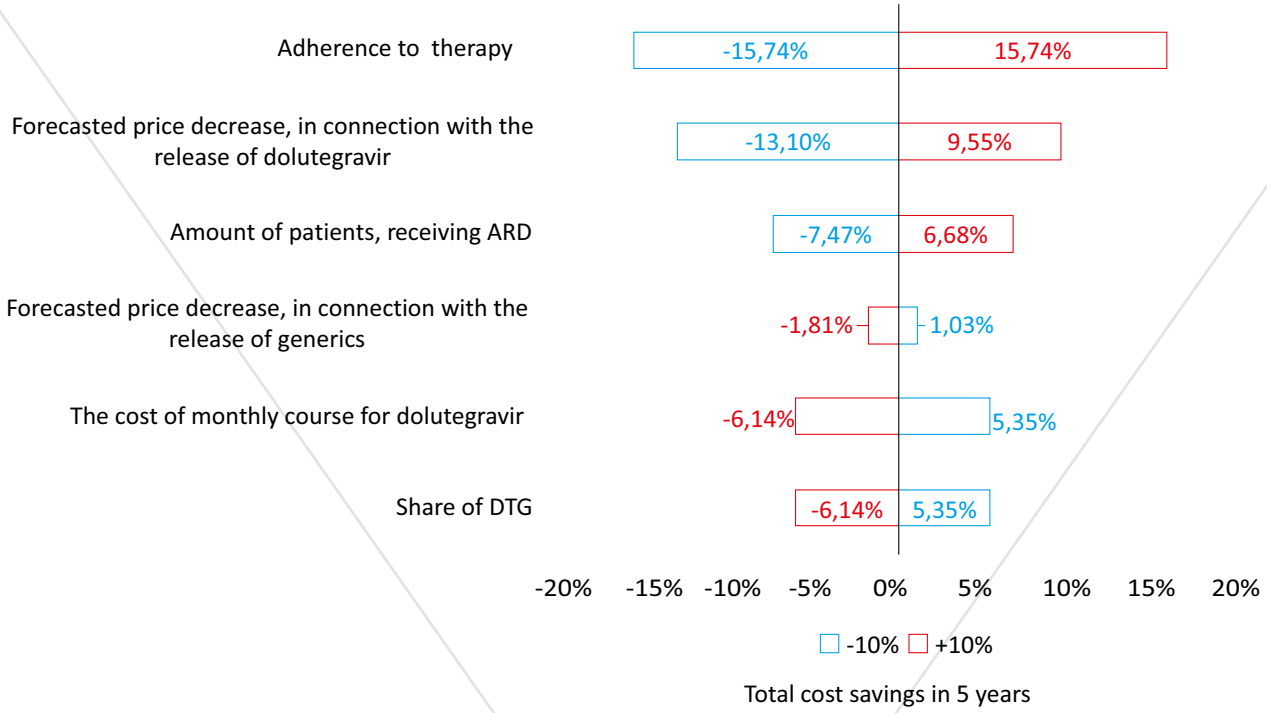

Figure 2. Stress test results: the impact of the change in input data within +/-10% of the original values for total cost savings over a five-year period

treatment; take into account the direct non-medical costs associated with the treatment of HIV infection, the complications of HIV infection, and the adverse side effects that arise from the treatment; take into account the indirect costs associated with the development of HIV-positive complications; take into account the indirect costs associated with the spread of HIV infection; to discount the results obtained; to consider in a holistic manner the budget of the HIV treatment program, as the reduction/increase in the procurement of the third-party components of ART may be affected by the reduction/increase in the acquisition of the basic components of ART; take into account possible price reductions based on trends in the baseline period.

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