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JULUCA - a new therapeutic opportunity for patients infected with HIV-1

**Krystian Cholewa¹, Julita Poleszak^{1,*}, Olga Wysokińska¹, Adam Gędek¹,
Bartłomiej Zaremba¹, Przemysław Szabat¹, Joanna Milanowska²**

¹Student Science Club at the Department of Applied Psychology, Medical University of Lublin, Poland

²Department of Applied Psychology, Medical University of Lublin, Poland

*E-mail address: julita.poleszak@wp.pl

ABSTRACT

Although there are currently known treatments for AIDS patients, the virus is still evolving, which means that it is not always possible to eradicate it from an infected organism. The FDA approved in November 2017 the first, complete treatment regimen containing two drugs: dolutegravir and rilpivirine (Juluca). The following article discusses current knowledge about a new, innovative drug as well as future therapeutic options of HIV-1 patients. The preparation can be used as a complete treatment regimen for HIV-1 infection to replace the current antiretroviral regimen in adults who have been virologically inhibited for at least 6 months. Clinical studies of this preparation show that the drug is well tolerated, is metabolizable and offers additional benefits, such as improving the lipid profile, improving bone mineral density and reduced bone resorption. Undoubtedly, longer observation of the effects of this drug therapy is needed, but this dual scheme seems to be a promising strategy for patients infected with HIV.

Keywords: HIV, AIDS, Juluca, new treatment, dolutegravir, rilpivirine

1. INTRODUCTION

In order to treat adults with HIV-1 infection, the FDA approved in November 2017 the first complete therapy regimen containing two drugs [1]. Initially, effective double combinations were based on protease inhibitors, but when Dolutegravir (DTG), the first integrase inhibitor was commercially available, many doctors began using it in a variety of dual schemes, generating several observation groups. This approval marks the beginning of a new era in the treatment of HIV, leading to the combination of Dolutegravir and Rilpivirine (RPV) combination – called Juluca. Currently, Juluca is indicated as a complete treatment regimen of HIV-1 infection in adults, in order to replace the current schedule of antiretroviral treatment in people who are virologically inhibited for at least 6 months.

The following article discusses current knowledge about a new, innovative drug – Juluca, as well as future, therapeutic options for HIV-1 patients.

2. HIV VIRUS

HIV – human immunodeficiency virus is a retrovirus classified as a type of letinivirus. Antigenic differences allowed to distinguish between two types of virus: HIV-1, and HIV-2, each of which can be divided into groups. These are successively M, N, O, P for HIV-1, and A-H for HIV-2 [2, 3]. The most common virus group is M HIV-1, which is divided into subtypes A to D, from F to H, J and K. We also distinguish recombinant HIV viruses from different subtypes [4].

HIV Virion is of a spherical shape and its diameter is 100-150 nm [5]. It is made of a lipid capsule and a core. The lipid envelope consists of two glycoproteins. The transmembrane glycoprotein g41 and the epidural glycoprotein gp120 form monomers that, when combined into trimers, are crucial for infection with HIV galls.

The capsid is a container consisting of approx. 4000 atoms, which form about 1300 identical CA capsid proteins. They build pentamers and hexamers, which form an irregular structure [6].

The CA protein is a monomer composed of two independent domains: the N-terminal domain of 150 amino acids (CANTD) and the C-terminal domain of ~ 80 amino acids (CACTD). Inside this core, there are two copies of the viral RNA genome, reverse transcriptase, integrase, HIV protease, nucleocapsid proteins, and viral helper proteins 9-11 [7]. The genome of HIV includes the following genes: gag, pol, env, tat, rev, nef, vif, vpr, tev, which encode a total of 19 proteins [8].

The CD4 receptor on the host cell is the site to which the glycoprotein gp120, which is part of the virus envelope, is attached. After combining the cell with the pathogen, the chemokine co-receptors react (mainly CCR5 or CXCR4), which triggers irreversible conformational changes [9, 10]. They enable the fusion and release of the virus genome. There RNA is reverse transcribed due to the presence of its own reverse transcriptase. Integrase along with DNA repair enzymes introduce the virus genome into the chromosomal host DNA. The cell becomes the producer of the virus.

The final stages of virus production require the transcription of the altered genome and the transport of viral particles towards the cell membrane where it is deposited. Then virus can leave the cell by budding.

For HIV, three routes of infection are characteristic: through sexual contact, contact with infected body fluids, and during pregnancy, delivery or breastfeeding (so-called vertical transmission). There is no risk of acquiring HIV in the case of exposure to faeces, nasal discharge, saliva, sputum, sweat, tears, urine or vomit unless they are contaminated with blood [11].

The course of HIV infection varies. It depends on the interaction between the virus and the patient's body. An important role here is attributed to genetic factors, elements of the immune system, and cytokines. The risk of infection depends on the type of exposure, virulence of a given strain of a virus, viral load and the so-called cellular tropism of the virus. The rate of development of the disease is influenced by the ability of the virus to escape from the immune system and the rate of destruction of the immune system [12].

The first infection is covered by T cells and macrophages leading to viral load and lymphoid tissue involvement. The immune system, however, controls the defense response of the body. The patient enters a latent state, the virus replicates. The asymptomatic period may last several years. It is followed by significant deterioration of the immune system, opportunistic infections, and malignant tumors.

Acquired Immunodeficiency Syndrome (AIDS) is a symptomatic phase of HIV infection. About 6 months after the primary infection, the infection enters the asymptomatic stage. Chronic activation of the immune system followed by CD4 + cell apoptosis. We speak about the early symptomatic phase when the CD4 + cell count falls below 500 cells / μ l. Over time, the number of blood cells continues to decrease and opportunistic infections and malignant tumors may appear.

3. EPIDEMIOLOGY OF HIV INFECTIONS IN POLAND AND IN THE WORLD

It is estimated that the number of living people infected with HIV is 36 900 000, the most of which come from southern and eastern Africa. Immediately behind them are the inhabitants of Southeast Asia, the Americas, Europe, the Western Pacific and the Mediterranean region (figure 1) [13]. The number of new infections per year shows a declining trend in the world (2000 - 3 million new infections, 2016 - 1.8 million), however, in Eastern Europe and Central Asia this rate increases significantly from year to year [14]. The global number of deaths related to AIDS is also falling (between 2003 and 2016 a decrease of about 46% was noted), which is associated with the increasingly widespread use of HIV therapies that prolong the lives of patients and which are decidedly more often decided by women than men [15].

Infections occur primarily in cities, and the highest-risk groups include drug addicts using injecting drugs (primarily in China, the USA, and Russia), prisoners, men having sex with other men, transgender and prostituted persons [16]. In addition, men over the age of 25 are infected (39% of all infections). In Poland, the number of HIV infected increases significantly with each year (2000 - 630 new infections, 2017 - 1526) and mainly concerns the age group 20 - 39. Despite this, it was observed that the incidence of AIDS and mortality is definitely decreasing [15]. The most common causes of infections among Poles include drug injections and homosexual contacts (men), while the rarest ones are iatrogenic and vertical roads. They occur mainly in the following provinces: Mazowieckie and Dolnośląskie, while the lowest rates of infection were recorded in the east, mainly in the Podkarpackie and Świętokrzyskie voivodships.

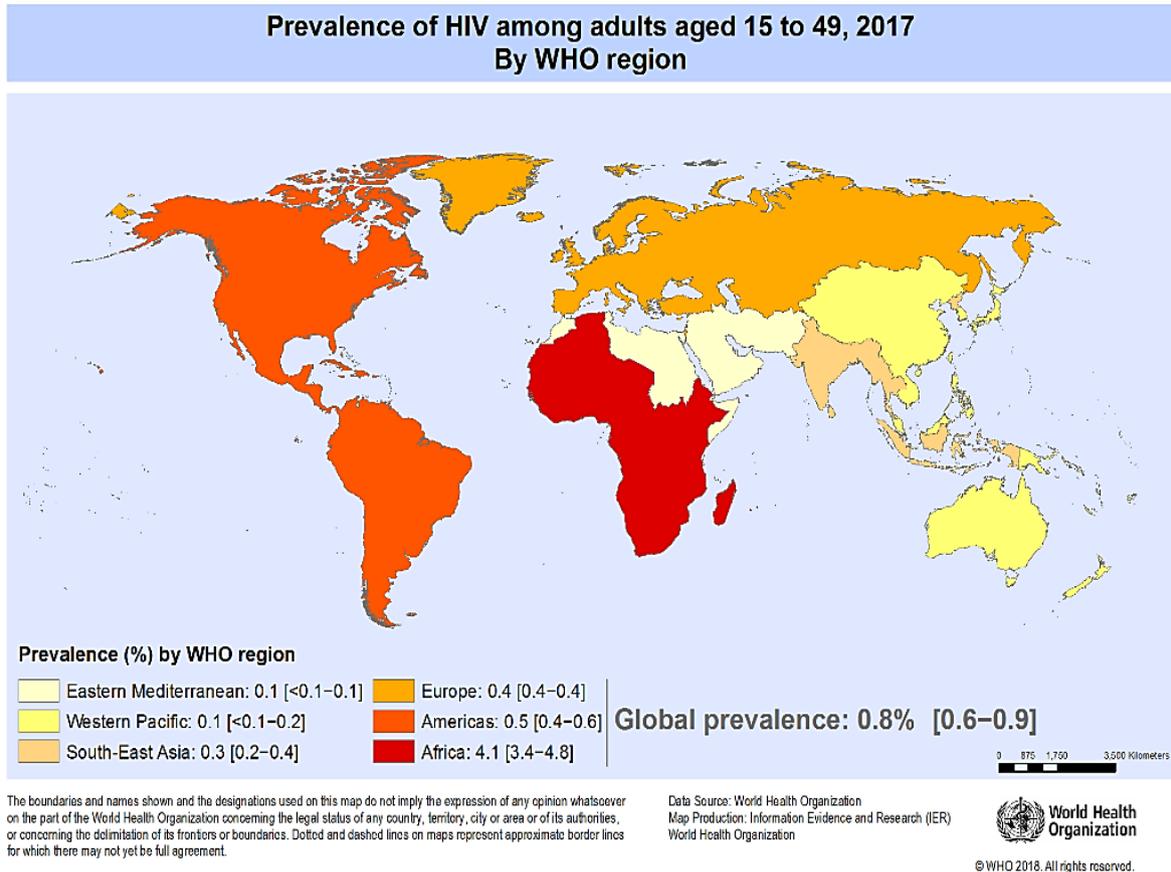


Figure 1. Prevalence of HIV on the world by WHO
(<https://www.who.int/gho/hiv/en/>)

4. JULUCA

Juluca is a breakthrough drug in the treatment of HIV infection because it is the first drug which affect the two stages of viral replication [18]. It is a new therapeutic option for over 10 000 people covered by antiviral therapy in Poland. It gives patients infected with HIV the possibility of taking only one tablet once a day, which significantly increases the comfort of their lives, and reduces the risk of side effects.

Treatment with this medicinal product is indicated in patients who have received combination therapy for HIV for at least 6 months and achieved viral loads (amount of HIV-1 virus in the blood) below 50 copies/ml. It cannot be used in patients who have failed during treatment with any anti-HIV drug or those who are HIV-positive (with HIV which is resistant to drugs that work in the same mechanism as the active substances in Juluca) [19].

The current treatment regimen is based on the cART scheme - combined antiviral therapy. It consists in the use of several drugs with synergistic action, which makes possible to inhibit the multiplication of the virus. The most commonly used combination of drugs is two NRTIs (nucleoside reverse transcriptase inhibitors) in combination with NNRTI (a non-nucleoside

reverse transcriptase inhibitor) or PI (a protease inhibitor) reinforced with Ritonavir or INSTI (an integrase inhibitor). In addition to the above, there are other alternative preparations [20].

Each drug acts on a different stage of HIV replication, beginning with its entry into the cell, by prescribing genetic information, the synthesis of viral proteins, ending with release from the virion-cell, capable of infecting further cells. On the basis of this, several groups of drugs have been distinguished: nucleoside reverse transcriptase inhibitors (NRTIs) - competitively block the reverse transcriptase enzyme; non-nucleoside reverse transcriptase inhibitors (NNRTIs) - bind directly to reverse transcriptase and inactivate its catalytic site; protease inhibitors (PI) - they combine with the active site of the protease and inhibit proteolytic activity, as a result of which the resulting copies of the virus are immature and non-infectious; integrase stand transfer inhibitor (INSTI) - prevent the transfer of DNA strand from the nucleus to the cytoplasm by the attachment of divalent cations present in the central catalase of integrase.

These cations are necessary for the interaction of the enzyme with host cell DNA; fusion inhibitors (FIs) - combine with the GP41 viral glycoprotein, which in turn blocks the process of HIV fusion with the host cell; CCR5 co-receptor inhibitors (CCR5 antagonists) - antagonize the CCR5 receptor, which is present mainly on T lymphocytes, macrophages and dendritic cells, preventing the combination of the GP120 viral glycoprotein with this receptor, which inhibits the virus's entry into these cells (Table 1).

Table 1. Groups of drugs for the treatment of HIV-infection.

Groups of drugs	Mechanism of action	Effect of action
nucleoside reverse transcriptase inhibitor – NRTIs	competitively block the reverse transcriptase enzyme	interrupting the life cycle of HIV
non-nucleoside reverse transcriptase inhibitor – NNRTIs	bind directly to reverse transcriptase and inactivate its catalytic site	stop the virus from replicating itself
protease inhibitor – PI	inhibit proteolytic activity of the protease	copies of the virus are immature and non-infectious
integrase stand transfer inhibitor – INSTI	attachment of divalent cations present in the central catalase of integrase	prevent the transfer of DNA strand from the nucleus to the cytoplasm
Fusion inhibitors – FIs	combine with the GP41 viral glycoprotein	block the process of HIV fusion with the host cell
CCR5 antagonists	antagonize the CCR5 receptor on immune cells	inhibit the virus's entry into these cells

When selecting a treatment regimen, first of all, its effectiveness should be taken into account, understood as ensuring long-term suppression of virus replication. Relevant diseases (especially kidney and liver disorders), medication and possible drug interactions, as well as the patient's lifestyle, are also important.

Compounds made up of several active substances, such as two NRTIs or two NRTIs and one NNRTI, have so far been registered, but Juluca is a breakthrough product that is a total therapy and there is no need use it with other antiretroviral medicines.

The two active substances that make up Juluca are Dolutegravir and rilpivirine. Dolutegravir is an integrase inhibitor, whereas rilpivirine is a diaryl-pyrimidine non-nucleoside HIV-1 reverse transcriptase inhibitor. Importantly, rilpivirine does not inhibit human DNA polymerases. Juluca helps maintain HIV-1 viral load at an appropriately low level, increases the number of CD4 + lymphocytes in the blood, which is associated with the inhibition of the development of opportunistic infections typical of AIDS and reducing the risk of HIV transmission to others through, for example, sexual contact. The pharmaceutical form of the drug is a film-coated tablet containing 50 mg Dolutegravir and 25 mg rilpivirine, as well as excipients, including lactose. Juluca should be taken orally once a day [22].

Dolutegravir is rapidly absorbed after oral administration, the maximum concentration (T max) in the plasma reaches within 2 to 3 hours after administration of the drug, while the T max of rilpivirine is 4 to 5 hours. Juluca must be taken with food, as this is necessary for optimal absorption of rilpivirine. Taking a drug with a protein meal does not ensure adequate absorption of the drug.

Juluca is indicated for use in patients over 18 years of age because adequate data on the safety and efficacy of the medicine in younger patients has not been obtained. There is also no accurate information on the use of the preparation in elderly patients (65 years and more), but it is assumed that the dose should be the same as in younger adult patients [23].

Juluca is not recommended for use during pregnancy because the safety and efficacy of these patients have not been determined. In addition, the drug should not be used by women who are breastfeeding. However, it should be remembered that patients infected with HIV should not breastfeed at all, because this virus is excreted from the blood into breast milk.

In patients with mild or moderate renal impairment, there is no need to modify the dose (when creatinine clearance is greater than or equal to 30 mL/min) [24]. However, patients with severe renal impairment or with end-stage renal disease (ESRD) (when the creatinine clearance is lower than 30 mL/min) should be particularly observed for side effects and deterioration of health.

It is no necessary to modify the dose in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). However, there is no research about the use of Juluca in patients with severe hepatic impairment (Child-Pugh Class C), and therefore these therapies are not recommended.

The components of Juluca show a lot of drug interaction, so this preparation should not be used in patients who also use: dofetilide (anti-arrhythmic medicine); carbamazepine, oxcarbazepine, phenobarbital, phenytoin (used in the treatment of epilepsy and seizures); rifampicin, rifapentine (used to treat bacterial infections); omeprazole and other proton pump inhibitors used in the treatment of stomach ulcers, heartburn, gastroesophageal reflux disease; dexamethasone (a glucocorticosteroid mainly used to treat inflammation and allergic reactions) taken orally or as an injection, except once; medicines that contain St John's Wort (preparations of plant origin used to treat depression) [25].

For studying the antiviral effect of Dolutegravir, PBMC (peripheral blood mononuclear cells) and MT-4 cells were used in various laboratory strains [26]. The IC50 (inhibitory concentration) value in the PBMC cell assay was 0.5 nM and for MT-4 cells it remained in the 0.7-2 nM range. Similar IC50 results were obtained in the study of HIV-1 strains and various

of their clinically isolated subtypes. In contrast, the mean IC₅₀ value for 3 selected strains of HIV-2 was 0.18 nM (range from 0.09 to 0.61). A similar study on T cell lines was made for Rilpivirine. The median IC₅₀ for HIV-1 / IIB was 0.73 nM, while for HIV-1 strains of group M, the IC₅₀ range was 0.07-1.01.

The antiviral activity of rilpivirine weakens the presence of alpha-1-acid glycoprotein (1 mg/ml), human serum albumin (45 mg/ml) and 50% human serum.

In vitro studies have shown a high degree of binding of Dolutegravir to human plasma proteins, which is over 99% [27]. According to the population pharmacokinetic analysis, the average volume of drug distribution in HIV-infected patients is 17-20 L. The concentration of Dolutegravir does not affect the degree of its binding to plasma proteins. However, the concentration of unbound Dolutegravir plasma fraction increases when serum albumin is low (<35 g/l). This particularly applies to patients with impaired liver function. Dolutegravir passes into the cerebrospinal fluid, as well as to the male and female sexual organs - it is present in the fluid from the cervix and vagina, the tissue of the cervix and vaginal tissue, in the semen, in the rectum tissue. Rilpivirine also binds to a large extent with plasma proteins, mainly albumin. The in vitro binding degree is 99.7%. In contrast, the concentration of rilpivirine in other compartments than blood plasma has not been studied.

The UGT1A1 enzyme plays the major role in the metabolism of Dolutegravir, which catalyzes the process of drug glucuronidation. CYP3A has a small proportion of cytochrome. While rilpivirine is mainly metabolised by in vitro studies with cytochrome CYP3A. The terminal elimination half-life is about 14 hours for Dolutegravir and is three-fold lower than for rilpivirine, which is about 45 hours. Dolutegravir and Rilpivirine are mostly excreted in the form of metabolites in the faeces, whereas urinary excretion is 32% of the total oral dose and 6.1% respectively.

5. CLINICAL TESTS OF JULUCA

Based on data from two 3-phase studies SWORD, Juluca received FDA recognition. The SWORD -1 and 2 studies are independent, identical, randomized, multi-center and open [28]. The work was aimed at assessing the effectiveness of the transition from the 3-component antiretroviral treatment (CAR) to a 2-component drug. The study involved 1 027 patients who had previously achieved stable viral suppression for at least six months in other antiretroviral regimens. Recruits had no history of virological failure or known resistance to dolutegravir or rilpivirine. The research began in April 2015 and their planned end is August 2021.

The experiment was divided into the phase of early and late switching. The research group was selected to receive DTG 50 mg + RPV 25 mg for two phases (148 weeks). While the control group in the first phase (the first 52 weeks) was taken CAR, and the eligible participants switched to DTG 50 mg + RPV 25 mg once a day during the late switching phase (from 52nd week 148). CAR contained the following combinations: 2 NRTI + 1 INI, 2 NRTI + 1 NNRTI or 2 NRTI + 1PI. Plasma samples were collected on day 1, week 4, 8, 12, 24, 36 and 48. The main parameter studied was the percentage of participants with the ribonucleic acid (RNA) of HIV-1 amount <50 copies/milliliter (c / ml) at week 48.

Treatment of DTG + RPV was considered as not worse than CAR if the lower end of the bilateral 95% confidence interval for the difference between the two groups in response rates at week 48 is above 10% (Cochran-Mantel Haenszel test).

The target-treated population (ITT-E) consisted of all randomly assigned participants who received at least one dose of the study medication.

Secondly, over 30 parameters were monitored. Among others, level of satisfaction with treatment (HIV TSQ questionnaire), analysis of lipids, maximum baseline chemical toxicity after 48 weeks (ALT, albumin, ALP, AST, total bilirubin, chloride, creatinine, glucose, potassium, phosphate, sodium, BUN, total dioxide carbon, lipase, creatine phosphokinase and creatinine clearance), maximum baseline haematological toxicity (to assess hemoglobin, hematocrit, basophils, eosinophils, lymphocytes, monocytes, neutrophils, MCV, RBC count, white blood cell count and platelet count), adverse events medical, CD4 + lymphocyte count, HOMA-IR index, alkaline phosphatase serum level, IL-6 content, cystatin C, D-dimers, RBP, B2M and others.

The results showed that Juluca and 3-drug CAR achieve similar viral suppression (HIV-1 RNA <50 c / ml) in 48 weeks in both studies (Dolutegravir + Rilpivirine 486/513 (95%), CAR 485/511 (95%), adjusted difference -0.2%, (95% CI: [2.5%, - 3.0%])). Indicators of virological failure were <1% after treatment with DTG + RPV and 1% for CAR therapy. Hopes for a new therapy are that no mutations associated with resistance to the INSTI or clinically significant resistance to rilpivirine have been reported so far. The proportion of patients who discontinued treatment due to an adverse event (AE) was 4% in those receiving DTG + RPV once daily and less than 1% in patients undergoing CAR therapy. The most common AEs leading to withdrawal were mental disorders in 2% receiving DTG + RPV and <1% of administered CARs. The most common AEs (all grades) reported in at least 2% of patients were diarrhea and headache. Other very common side effects are insomnia, dizziness, increased total and LDL cholesterol on an empty stomach, nausea, increased activity of pancreatic amylase, increased transaminases. Based on data from Phase IIb and Phase III trials, it was shown that the most serious one-patient-related adverse event probably caused by Dolutegravir was a hypersensitivity reaction associated with skin rash and severe hepatic impairment.

The SWORD attempts are ongoing and will continue until the 148th week. The original reports are promising, long-term observations and analyzes are unknown, but they arouse curiosity. The long-term effect of the new drug on changes in bone mineral density (BMD) is unknown, but the substitution study showed an average BMD value increased from baseline to week 48 in people who switched antiretroviral therapy (ART) containing Tenofovir Disoproxil Fumarate (TDF) to Juluca (1.34% of the total hip and 1.46% of the lumbar spine) compared to those who continued treatment with the ART scheme containing TDF (0.05% of the total hip and 0.15% of the lumbar spine).

From June 2015. until August 2018. another study was organized on a group of 102 patients included in the SWORD-1 and 2 trials [29]. The aim of this study is to evaluate any changes in the baseline bone mineral density (BMD) in patients with a triple antiretroviral therapy (ART) regimen containing Tenofovir Disoproxil Fumarate (TDF) to Dolutegravir plus Rilpivirine. Patients participating in the study had DEXA scans taken on day 1 and in the weeks 48, 100 and 148. BMD determined in DEXA scans of the "lumbar spine", which included the first lumbar spine (L1) to the fourth lumbar vertebra (L4). The difference is the adjusted percentage change from the value on the beginning to week 48. To compare the difference in percentage changes, the ANCOVA model was used.

In studies on an animal model, it was shown that the preparation is not teratogenic. However, it has been proven that one of the components - Dolutegravir - causes defects in the fetus. Neural tube defects are diagnosed when the neural tube does not fully form up to 28 days

after fertilization and the spinal cord, the brain, as well as related structures do not develop properly. The Tsepamo study in Botswana has so far shown that in a newborn woman born at the time of conception, Dolutegravir has a defect with a frequency of 0.9% compared to a baseline of approximately 0.1%. The basal rate refers to newborns born to women who receive other anti-retroviral drugs during the period of conception. Therefore, women of childbearing age should undergo a pregnancy test to exclude pregnancy before starting therapy with Dolutegravir, and then they are required to use effective contraception during treatment.

There are also great expectations regarding the ongoing phase III clinical trials of Dolutegravir and Lamivudine. It is expected that new and future single component preparations with double regimens will improve their suitability.

6. CONCLUSIONS

Antiviral treatment for many years arouses the interest of scientists, because the previously adopted treatment methods still show some disadvantages. To reduce the toxicity and burden of antiviral drugs, researchers assess the efficacy, safety and durability of dual therapies as an option to change treatment in people who have achieved stable virological suppression. Currently, the most hope is the therapy consisting of two drugs enclosed in one tablet: dolutegravir and rilpivirine (Juluca). Clinical studies of this preparation show that the drug is well tolerated, is good for metabolism and offers additional benefits. Research suggest improvement in the lipid profile, improvement of bone mineral density and reduced bone resorption. Undoubtedly, longer observation of the effects of this drug therapy is needed, but this dual scheme seems to be a promising strategy for patients infected with HIV.

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