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DOVATO - A NEW DRUG FOR HIV INFECTION – REVIEW

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ABSTRACT

Human immunodeficiency virus infection (HIV) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV). HIV is spread primarily by unprotected sex, contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Dovato is the first FDA-approved two-drug, fixed-dose, complete regimen for HIV-infected adults who have never received treatment for HIV. The FDA granted approval of Dovato to ViiV Healthcare in April 2019. It is a fixed-dose combination product containing 50 mg of dolutegravir and 300 mg of lamivudine. In clinical trials, 91% of people who took Dovato shows decrease in HIV infection. Dolutegravir is an antiretroviral agent for HIV-1. It inhibits the integrase of HIV by binding to the active site and blocking the step of transferring the retroviral DNA integration filament into the host cell. The filament transfer phase is essential in the HIV replication cycle and leads to the inhibition of virus activity. Lamivudine is incorporated into the viral DNA by HIV reverse transcriptase and HBV polymerase, resulting in the termination of the DNA chain. It shows less side effects as compared to other drugs. Dovato is a complete regimen for the treatment of HIV infection and should not be used with other HIV medicines.

KEY WORDS: Dovato, Dolutegravir, Lamivudine, Human immunodeficiency virus infection (HIV)

INTRODUCTION

HIV stands for Human Immunodeficiency Virus. It is the virus that can lead to acquired immunodeficiency syndrome or AIDS if not treated. Unlike some other viruses, the human body can't get rid of HIV completely, even with treatment. So once you get HIV, you have it for life.

HIV attacks the body's immune system, specifically the CD4 cells (T cells), which help the immune system fight off infections. Untreated, HIV reduces the number of CD4 cells (T cells) in the body, making the person more likely to get other infections or infection-related cancers. Over time, HIV can destroy so many of these cells that the body can't fight off infections and disease. These opportunistic infections or cancers take advantage of a very weak immune system and signal that the person has AIDS, the last stage of HIV infection.[1]

HIV can transmit only through specific activities. Most commonly, people get or transmit HIV through sexual behaviors and needle or syringe use.

Only certain body fluids—blood, semen, pre-seminal fluid, rectal fluids, vaginal fluids, and breast milk—from a person who has HIV can transmit HIV. These fluids must come in contact with a mucous membrane or damaged tissue or be directly injected into the bloodstream (from a needle or syringe) for transmission to occur.[1]

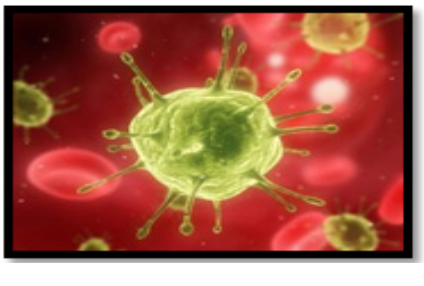

FIG:1 HIV VIRUS

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- Sharing needles or syringes, or other equipment (works) used to prepare drugs for injection with someone who has HIV. HIV can live in a used needle up to 42 days depending on temperature and other factors.
- From mother to child during pregnancy, birth, or breastfeeding.
- Receiving blood transfusions, blood products, or organ/tissue transplants that are contaminated with HIV.

These are the stages and symptoms of HIV:

Stage 1 (Acute HIV infection): Within 2 to 4 weeks after infection with HIV, about two-thirds of people will have a flu-like illness. This is the body's natural response to HIV infection. Flu-like symptoms can include: fever, chills, rashes, night sweats, muscle aches, sore throat, fatigue, swollen lymph nodes and mouth ulcers.

Stage 2 (Clinical Latency): In this stage, the virus still multiplies, but at very low levels. People in this stage may not feel sick or have any symptoms. This stage is also called chronic HIV infection. Without HIV treatment, people can stay in this stage for 10 or 15 years.

Stage 3 (AIDS): This is the late stage of HIV infection. The virus will weakens body's immune system and will progress to AIDS (Acquired ImmunoDeficiency Syndrome). The symptoms are given below:

- Rapid weight loss
- Recurring fever or profuse night sweats
- Extreme and unexplained tiredness
- Prolonged swelling of the lymph glands in the armpits, groin, or neck
- Diarrhea that lasts for more than a week
- Sores of the mouth, anus, or genitals
- Pneumonia
- Red, brown, pink, or purplish blotches on or under the skin or inside the mouth, nose, or eyelids
- Memory loss, depression, and other neurologic disorders.[1]

There are three types of tests that can confirm HIV infection:

- NAT (Nucleic Acid Testing), looks for the actual human immunodeficiency virus in the blood. But this expensive test is rarely used for routine screening.
- An antigen/antibody test looks for HIV antibodies, which are proteins produced by the immune system after exposure to bacteria or viruses. The blood test also detects HIV antigens — foreign substances that activate the immune system.
- The third type is an antibody test that looks for HIV antibodies in blood or oral fluid. These tests can be done with a kit at home and provide results usually within 30 minutes.[2]

The FDA has approved more than two dozen antiretroviral drugs to treat HIV infection. Some of them are given below:

- Abacavir, or ABC (Ziagen)
- Didanosine, or ddl (Videx)
- Emtricitabine, or FTC (Emtriva)
- Stavudine, or d4T (Zerit)
- Tenofovir alafenamide, or TAF (Vemlidy)
- Tenofovir disoproxil fumarate, or TDF (Viread),
- Zidovudine or ZDV (Retrovir)
- Delavirdine or DLV (Rescripor)
- Doravirine, or DOR (Pifeltro)
- Efavirenz or EFV (Sustiva)

Although these drugs shows some side effects such as trouble sleeping or loss of appetite, trouble breathing, overactive thyroid, swollen lymph nodes, joint pain, headache, weight loss, vision changes etc..[3]

The FDA has approved a new drug for HIV infection called DOVATO in April 2019.

Dolutegravir/Lamivudine (Rx)

FIG: 2 LABELLING OF DOVATO

- Brand and Other Names: Dovato
- Classes: HIV, ART Combos

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Dovato is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg.

Dovato does not cure HIV infection or AIDS, but it may hold off damage to the immune system and the development of infections and disease associated with AIDS.4

Dovato is a once-daily, single-tablet, two-drug regimen that combines the integrase strand transfer inhibitor (INSTI) dolutegravir (Tivicay, 50 mg) with the nucleoside analogue reverse transcriptase inhibitor (NRTI) lamivudine (Epivir, 300 mg).

Dovato is specifically indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to the individual components of Dovato.

Dovato is supplied as a tablet for oral administration. It is a fixed-dose combination product containing 50 mg of dolutegravir and 300 mg of lamivudine. The recommended dosage regimen in adults is one tablet taken orally once daily with or without food.

The dolutegravir dose (50 mg) in Dovato is insufficient when co-administered with drugs listed below that may decrease dolutegravir concentrations; the following dolutegravir dosage regimen is recommended:

- Co-administered Drug: Carbamazepine, Rifampin
- Dosing Recommendation: An additional dolutegravir 50-mg tablet, separated by 12 hours from Dovato, should be taken.
- Dovato is not recommended in patients with renal impairment or severe hepatic impairment.[5]

DOSAGE FORMS AND STRENGTH

Dovato is available as tablets containing 50mg of dolutegravir and 300mg of lamivudine

FIG: 3 DOVATO TABLET

ADMINISTRATION

- Oral administration.
- May take with or without food.
- Missed dose: Instruct patients to take a missed dose as soon as they remember, but do not double their next dose or take more than prescribed.[6]

MECHANISM OF ACTION

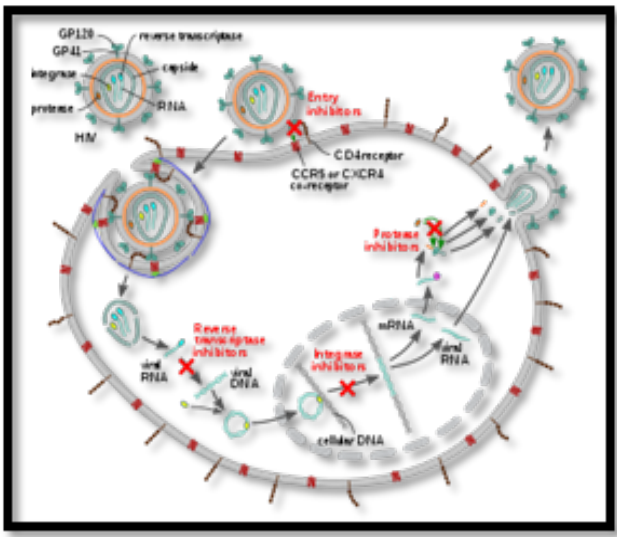

FIG: 4 MECHANISM OF ACTION OF DOVATO

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

Lamivudine, via its active metabolite 5'-triphosphates (TP) (an analogue for cytidine), inhibits reverse transcriptase of HIV-1 and HIV-2 through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Lamivudine triphosphate shows significantly less affinity for host cell DNA polymerases.[7]

PHARMACOLOGY

Absorption

Dolutegravir and lamivudine are rapidly absorbed on oral administration. The absolute bioavailability of dolutegravir has not been established. The absolute bioavailability of oral lamivudine in adults is approximately 80-85%. For Dovato, the median time to maximal plasma concentration (tmax) is 2.5 hours for dolutegravir and 1.0 hour for lamivudine, when dosed under fasted conditions.[7]

Distribution

The apparent volume of distribution of dolutegravir (Vd/F) is 17-20 L. Intravenous studies with lamivudine showed that the mean

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apparent volume of distribution is 1.3 L/kg
Dolutegravir is highly bound (> 99%) to human plasma concentration. Binding of dolutegravir to plasma proteins is independent of dolutegravir concentration. The unbound fraction of dolutegravir in plasma is increased at low levels of serum albumin. Lamivudine exhibits linear pharmacokinetics over the therapeutic dose range and displays limited plasma protein binding.[7]

Metabolism

Dolutegravir is primarily metabolized via UGT1A1 with a minor CYP3A component (9.7% of total dose administered in a human mass balance study). Dolutegravir is the predominant circulating compound in 20 plasma. Renal elimination of unchanged active substance is low (< 1% of the dose). Fifty-three percent of total oral dose is excreted unchanged in the faeces.
Lamivudine were not significantly metabolized.[7]

Excretion

Dolutegravir is primarily metabolized and eliminated by the liver. Fifty-three percent of total oral dose is excreted through faeces. Thirty-two percent of the total oral dose is excreted in the urine. Lamivudine is predominately cleared by renal excretion. The likelihood of metabolic drug interactions with lamivudine is low due to the small extent of hepatic metabolism.[7]

SIDE EFFECTS/ADVERSE EFFECTS

The most common side effect with Dovato (which may effect up to 1 in 10 people) are headache, diarrhoea, nausea and difficulty in sleeping. The most common serious side effect (which may affect up to 1 in 100 people) are allergic reactions including rashes and severe liver problems.
The Dovato drug label comes with the following

Black Box Warning: All patients with HIV-1 should be tested for the presence of HBV prior to or when initiating Dovato. Emergence of lamivudine-resistant HBV variants associated with lamivudine-containing antiretroviral regimens has been reported. If Dovato is used in patients co-infected with HIV-1 and HBV, additional treatment should be considered for appropriate treatment of chronic HBV; otherwise, consider an alternative regimen. Severe acute exacerbations of HBV have been reported in patients who are co-infected with HIV-1 and HBV and have discontinued lamivudine, a component of Dovato. Closely monitor hepatic function in these patients and, if appropriate, initiate anti-HBV treatment.[5]

CONTRAINDICATIONS

Pregnancy

Dolutegravir: Avoid use at the time of conception through the first trimester owing to risk of neural tube defects associated with dolutegravir; advise individuals of childbearing potential to consistently use effective contraception

Lamivudine: Based on prospective Antiretroviral Pregnancy Registry (APR) reports, resulting in live births, there was no difference between the overall risk of birth defects for lamivudine compared with the background birth defect rate of 2.7% in the US reference population Serious cases of neural tube birth defects involving the brain, spine, and spinal cord reported in babies born to women treated with dolutegravir

Preliminary results from an ongoing observational study in Botswana found women who had received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects; to date, in this observational study there are no reported cases of babies born with neural tube defects to women starting dolutegravir later in pregnancy.[6]

Lactation

Breastfeeding is not recommended because of potential for HIV-1 transmission from mother to infant.
The Centers for Disease Control and Prevention recommend that HIV-1-infected mothers in the United States do not breastfeed infants to avoid risk of postnatal transmission of HIV-1 infection; unknown whether drug is present in human breast milk, affects human milk production, or has effects on breastfed infant; when administered to lactating rats, dolutegravir was present in milk
Because of potential for (1) HIV-1 transmission (in HIV-negative infants) and (2) developing viral resistance (in HIV-positive infants), instruct mothers not to breastfeed if they are receiving drug therapy.[6]

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DRUG INTERACTIONS

- Antacids or laxatives that contain calcium, magnesium, or aluminum (such as Amphojel, Di-Gel Maalox, Milk of Magnesia, Mylanta, Pepcid Complete, Rolaids, Rulox, Tums, and others), or the ulcer medicine sucralfate (Carafate).
- Buffered medicine
- Vitamin or mineral supplements that contain calcium or iron (but if you take dolutegravir with food, you can take these supplements at the same time).
- Many drugs interact with dolutegravir and lamivudine. This includes prescription and over-the-counter medicines, vitamins, and herbal products.[8]

Examples;

- LAMIVUDINE/ZALCITABINE
- DOLUTEGRAVIR/DOFETILIDE
- DOLUTEGRAVIR/SELECTED UGT1 & CYP3A4 INDUCERS
- DOLUTEGRAVIR/SELECTED ORAL CATIONS

Clinical trials

The US FDA's approval for Dovato was based on the positive results obtained from two Phase III clinical trials named GEMINI 1 and GEMINI 2, which together enrolled 1,433 adult HIV-1 patients with no ARV treatment history.
Dovato was administered once daily for 148 weeks in patients with baseline HIV-1 viral loads up to 500,000 copies per millilitre during both the trials.

The drug was also compared to a three-drug regimen comprising dolutegravir, two NRTIs, and tenofovir disoproxil fumarate/emtricitabine (Truvada; TDF/FTC). The primary efficacy endpoint of each trial was the achievement of plasma HIV-1 RNA RiboNucleic acid (RNA) copies to less than 50 per ml after week 48 in 91% cases.

A mean change of 0.116mg/dl was observed in fasted lipid values of patients treated with a two-drug combination of dolutegravir and lamivudine from baseline to week 48. The mean change for patients treated with a three-drug regimen was noticed as 0.154mg/dl from baseline to week 48.

Dovato achieved a 10% non-inferior efficacy compared to the three-drug regimen during the trials and resulted in reducing exposure to the number of ARVs.
Insomnia, diarrhoea, headache, nausea, and fatigue were Dovato's most common adverse events noticed during the GEMINI I and II clinical trials.[9]

USES

Dovato contains two drugs; dolutegravir and lamivudine.They are used to help control HIV infection. It helps to decrease the amount of HIV in our body so our immune system can work better. This lowers your chance of getting HIV complications (such as new infections, cancer) and improves your quality of life. This medication is not a cure for HIV infection but helps in decrease in spreading of HIV disease.[10]

CONCLUSION

Dovato is a FDA approved new drug for treating HIV infection. It is a combination of two drugs, dolutegravir and lamivudine. Dovato combination was found to be as effective as a triple combination in patients with HIV-1, with no cases of resistance developing in the patients. In the studies , 91% of the patients with HIV-1 who took the Dovato combination no longer detected the levels of HIV. Dovato is more effective and has less side effect as compared to other HIV drugs.

REFERENCE

1. www.cdc.gov Retrieved from [https://www.cdc.gov/hiv/basics/whatishiv.html] Accessed on 23 October 2019
2. www.livescience.com Retrieved from [https://www.livescience.com/34699-hiv-aids-symptoms-treament-prevention.html] Accessed on 23 October 2019
3. www.webmd.com Retrieved from [https://www.webmd.com/hiv-aids/aids-hiv-medication] Accessed on 24 October 2019
4. www.ema.europa.eu Retrieved from [https://www.ema.europa.eu/en/medicines/human/EPAR/dovato] Accessed on 25 October 2019
5. www.centerwatch.com Retrieved from [https://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100373/dovato-dolutegravir-and-lamivudine-] Accessed on 25 October 2019
6. Reference.medscape.com Retrieved from [https://reference.medscape.com/drug/dovato-dolutegravir-lamivudine-1000318#10] Accessed on 28 October 2019
7. www.ema.europa.eu Retrieved from [https://www.ema.europa.eu/en/documents/product-information/dovato-epar-product-information_en.pdf] Accessed on 1 November 2019
8. www.drugs.com Retrieved from [https://www.drugs.com/dovato.html] Accessed on 1 November 2019
9. www.clinicaltrialsarena.com Retrieved from [https://www.clinicaltrialsarena.com/projects/dovato-dolutegravir-lamivudine/] Accessed on 2 November 2019
10. www.webmd.com Retrieved from [https://www.webmd.com/drugs/2/drug-177077/dovato-oral/details] Accessed on 3 November 2019

Cite this article: DOVATO -A NEW DRUG FOR HIV INFECTION – REVIEW Sci J Phar and Pharmaceu Sci. 2019; 1(2): 01-05.