Summary

Dolutegravir belongs to the class of drugs called integrase inhibitors and is meant to be used as part of combination therapy for the treatment of HIV. For most patients, dolutegravir can be taken at a dose of 50 mg once daily. This drug does not have any food or water restrictions and it can be taken day or night. Dolutegravir was relatively well tolerated in clinical trials. When side effects occurred, they were generally mild and temporary.

What is dolutegravir?

Dolutegravir, sold under the brand name Tivicay and in Juleuca and Triumeq, belongs to a class of anti-HIV (or antiretroviral) drugs called integrase inhibitors. Dolutegravir is used in combination with other anti-HIV drugs to treat, but not cure, HIV.

How does dolutegravir work?

This drug works by interfering with an enzyme needed by HIV called integrase. Using dolutegravir as part of combination therapy reduces HIV’s ability to infect cells and make copies of itself.

How do people with HIV use dolutegravir?

Dolutegravir is used in combination with several other anti-HIV drugs, usually nukes (nucleoside analogues), non-nukes (NNRTIs) and drugs from other classes, such as protease inhibitors. These combinations are called antiretroviral therapy, or ART. For more information on ART, see CATIE’s Your Guide to HIV Treatment.

For many people with HIV, the use of ART has increased their CD4+ cell counts and decreased the amount of HIV in their blood (viral load). These beneficial effects help to greatly reduce the risk of developing a life-threatening infection. Neither dolutegravir nor any other anti-HIV medication is a cure for HIV. It is therefore important that you see your doctor for checkups and lab tests on a regular basis.

Evidence shows that HIV-positive people who are on ART, engaged in care, and have an ongoing undetectable viral load are substantially less likely to transmit HIV to others, be it through sex, when sharing equipment to use drugs or during pregnancy and birth. In fact, the evidence for sexual transmission shows that people on ART who maintain an undetectable viral load do not pass HIV to their sexual partners. For further information see the CATIE fact sheet HIV treatment and an undetectable viral load to prevent HIV transmission. However, it is still a good idea to use condoms because they can reduce your risk for getting and passing on other sexually transmitted infections.

Warnings

Because dolutegravir is a relatively new medication (it was only approved in 2013), the full range of its side effects may not be known for many years.

Pregnancy

In May 2018, regulatory agencies issued cautionary statements because dolutegravir was associated with an apparent increased risk of birth defects in a clinical trial:

If you are taking dolutegravir and are pregnant or want to have a baby, speak to your doctor.

Hepatitis B or C viruses

People who are co-infected with hepatitis B or C viruses may develop increased levels of liver enzymes in the blood...
or intensified symptoms of infection with these viruses. Therefore, the manufacturer advises doctors to conduct “appropriate” laboratory testing before and during therapy with dolutegravir and to monitor patients for liver injury.

Other medicines

Dolutegravir causes few interactions with other drugs. However, there are other medicines that interfere with dolutegravir levels in the blood, usually decreasing them. See the section on Drug interactions below for more information.

Side effects

General

In clinical trials, dolutegravir, like all integrase inhibitors, was well tolerated, generally safe and effective. However, as with any treatment, there were side effects that users should be aware of. The most common side effects were as follows:

- headache
- difficulty falling asleep
- nausea
- diarrhea

Bear in mind that, like all new drugs, as dolutegravir becomes more widely used in the community, there may be reports of other side effects.

The kidneys

The kidneys filter the blood and then put waste materials into urine and reabsorb nutrients and other useful materials back into the blood.

Dolutegravir can interfere with the ability of the kidneys to release the waste product creatinine into urine. Therefore, a small but persistent increase of creatinine levels in the blood is generally seen in dolutegravir users. This small increase is not considered harmful. Furthermore, this effect on creatinine does not appear to affect the ability of the kidneys to filter other substances. Such an effect on creatinine is also seen with the anti-ulcer drug cimetidine (Tagamet) and with the boosting agent cobicistat, found in Stribild.

Uncommon side effects

1. Hypersensitivity

Hypersensitivity reactions occurred in less than 1% of participants in phase III clinical trials. Symptoms included severe rash or rash with a fever, together with lack of energy and painful muscles or joints. In severe cases additional symptoms occurred, such as peeling of the skin, blisters on the lips, swollen eyes and face, stomach cramps and difficulty breathing. The manufacturer advises that dolutegravir (or any other drugs suspected of causing this reaction) should be discontinued immediately if these symptoms occur, otherwise the hypersensitivity reaction can become life threatening. If symptoms suggestive of hypersensitivity occur, see your doctor immediately or go to the emergency room of your nearest hospital or medical centre.

In the rare cases of a hypersensitivity reaction to dolutegravir, the manufacturer advises that this drug should not be restarted.

2. Anxiety and depression

Note that all integrase inhibitors, including dolutegravir, have been associated with rare cases of anxiety and depression. Whether these drugs caused anxiety or depression is not clear. In some reports, the rare cases of anxiety and/or depression associated with the use of integrase inhibitors occurred mainly in people who had a history of these issues.

Anxiety and depression are relatively common in HIV-positive people (regardless of whether they are on treatment
or the type of treatment that they take). If you are taking dolutegravir and think that you may have developed anxiety or depression, speak to your doctor right away. Your doctor can help determine if you have anxiety or depression and if there is any relationship between them and the medicines that you are taking.

There have been reports of some people developing anxiety and/or depression after initiating treatment with dolutegravir. Symptoms of anxiety and depression can include the following:

- become easily upset or angry
- feel fearful
- excessive worry
- have unexpected feelings of sadness
- have prolonged feelings of sadness, anger or depression
- feel hopeless
- have loss of pleasure in everyday activities
- unexpectedly feel tired or experience a lack of energy
- have difficulty falling asleep, staying asleep or waking up prematurely
- have strange thoughts

If you have any of these feelings, contact your doctor or nurse.

If you have thoughts of harming yourself or others, dial 911 right away.

**Drug interactions**

In general, integrase inhibitors tend not to interfere with many other drugs (raising or lowering their levels in the blood). Dolutegravir causes few interactions with other drugs. However, there are other medicines that interfere with dolutegravir levels in the blood, usually decreasing them. Bear in mind that as dolutegravir becomes more widely used in the community, there may be reports of new drug interactions.

Here are recommendations from the manufacturer about potentially significant drug interactions with dolutegravir:

**Other HIV drugs**

Etravirine (Intelen) – this drug can reduce the concentration of dolutegravir in the blood. Therefore, the manufacturer recommends that dolutegravir should not be used with etravirine unless it is also taken with one of the following combinations of drugs:

- atazanavir (Reyataz) + ritonavir (Norvir)
- darunavir (Prezista) + ritonavir
- lopinavir + ritonavir (in Kaletra)

Nevirapine (Viramune) – dolutegravir should not be used with nevirapine, as there is not enough information to make dosing recommendations.

**Acid-reducing agents, laxatives, metal supplements and buffered medicines**

Dolutegravir should be taken 2 hours before or 6 hours after taking these medicines.

Examples of acid-reducing agents include:

- Alka-Seltzer
- Gaviscon (tablets and syrup)
- Maalox (liquid and tablets)
- Milk of Magnesia
- Pepto-Bismol and Pepto Bismol Children's
- Rolaid
- Tums
Metal supplements include those containing iron, calcium and magnesium.

**Abnormal heart rhythm drugs**

The drug dofetilide (Tikosyn) is prescribed to treat abnormal heart rhythms. Dolutegravir can raise levels of dofetilide. Although dofetilide is not approved in Canada, many Canadians travel to the U.S. where it is approved and may be prescribed this medicine. The manufacturer warns that dofetilide should never be used by patients who are taking dolutegravir, as high concentrations of dofetilide can occur causing serious injury.

**Anti-seizure drugs**

Oxcarbazepine, carbamazepine (Tegretol), phenobarbital, phenytoin (Dilantin) – dolutegravir should not be used with these drugs as there is not enough information to make dosing recommendations.

**Antibiotics**

Rifampin – this drug reduces the concentration of dolutegravir in the blood. The manufacturer recommends that dolutegravir at a dose of 50 mg twice daily should be used if rifampin must also be taken. However, the manufacturer also notes that in the case of patients who have used integrase inhibitors in the past and who have HIV that may be or is suspected to be resistant to integrase inhibitors, doctors and nurses should seek alternative antibiotics to rifampin where possible.

**Diabetes drugs**

Metformin – as dolutegravir can raise levels of metformin in the blood, the manufacturer recommends close monitoring of patients when they are starting or stopping therapy with dolutegravir. The manufacturer also suggests that it may be necessary to reduce the dose of metformin in some dolutegravir users.

**Herbs**

St. John’s wort (or compounds found in St. John’s wort such as hypericin, hyperforin) can significantly reduce dolutegravir levels and this herb should not be used. Although St. John’s wort is the only herb listed here, note that other herbs are likely to interact with dolutegravir.

**No interactions expected**

In clinical trials, dolutegravir did not have a clinically significant effect on the following drugs:

- tenofovir (Viread and in Truvada, Atripla, Complera and Stribild)
- methadone
- midazolam
- rilpivirine (Edurant and in Complera)
- oral contraceptives containing norgestimate and ethinyl estradiol

**Resistance and cross-resistance**

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes, called mutations, can cause HIV to resist the effects of anti-HIV drugs, which means those drugs will no longer work for you. Combining dolutegravir with at least two other anti-HIV drugs delays the development of drug resistance.

To reduce the risk of developing drug resistance, all anti-HIV drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed or not taken as prescribed, the level of dolutegravir in the blood may fall too low. If this happens, the HIV in your body can become resistant to the medication. If you find you are having problems taking your medications as directed, speak to your doctor, nurse or pharmacist about this. They can find ways to help you.

When HIV becomes resistant to one drug in a class, it sometimes becomes resistant to other drugs in that class. This is called cross-resistance. Feel free to talk with your doctor about your current and future treatment options. To help you decide what these future options might be, at some point your doctor can have a small sample of your blood analyzed to test for resistance. Should the HIV in your body become resistant to dolutegravir, your doctor
can recommend a new treatment combination for you.

For patients whose integrase inhibitor regimens are failing, doctors should request laboratory testing of their blood to assess the degree of resistance to integrase inhibitors. This will help doctors determine whether or not an integrase inhibitor can be used in future regimens.

A study in the U.S. with about 3,000 HIV-positive participants who were undergoing testing of their blood for the presence of HIV resistance has recently been completed. Researchers found that resistance to integrase inhibitors was present in 16% of participants. Their results suggested that, in most cases, dolutegravir would have “full or partial activity” against most strains of HIV with integrase resistance. However, 2% of all participants (or 12% of participants with HIV resistant to the integrase inhibitors raltegravir or elvitegravir) had “high-level resistance to dolutegravir.”

**Dosage**

Dolutegravir is available as a small 50-mg yellow tablet. Dolutegravir has been approved for use in people aged 12 years and older and who weigh at least 40 kg (88 pounds). It can be taken with or without food. There are two general dosing regimens for dolutegravir recommended by the manufacturer, as follows:

- People who have never previously used ART – 50 mg *once* daily
- People who have used ART but have never used an integrase inhibitor – 50 mg *once* daily
- People who have used integrase inhibitors and who have or are suspected to have resistance to other integrase inhibitors – 50 mg *twice* daily
- People who are taking any of these drugs (regardless of previous exposure to integrase inhibitors): efavirenz, fosamprevir + ritonavir, tipranavir (Aptivus) + ritonavir, and rifampin – 50 mg *twice* daily

**Availability**

Dolutegravir is licensed in Canada for the treatment of HIV infection in adults in combination with other anti-HIV drugs. Your doctor can tell you more about the availability and coverage of dolutegravir in your region. CATIE’s online module [Federal, Provincial and Territorial Drug Access Programs](https://www.catie.ca/drug-coverage) also contains information about Canadian drug coverage.

**REFERENCES:**


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Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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