

Triumeq

Summary

Triumeq is the name given to a pill containing the following three anti-HIV drugs: dolutegravir, abacavir and 3TC (lamivudine). Although Triumeq is usually well-tolerated, general side effects are uncommon and can include nausea, vomiting, diarrhea, headache and difficulty falling asleep. These are usually temporary and mild. Triumeq is a complete treatment in one pill and is taken once daily. Triumeq can be taken day or night, with or without food.

What is Triumeq?

Triumeq is the name of a pill that contains the following three anti-HIV drugs:

- dolutegravir (Tivicay and in Juluca), which belongs to a group or class of drugs called integrase inhibitors
- abacavir (Ziagen), which belongs to a group of drugs called nucleoside analogues or nukes
- 3TC (lamivudine), which belongs to a group of drugs called nukes

Triumeq is used as a once-daily, complete treatment for HIV infection.

How does Triumeq work?

When HIV infects a cell, it takes control of that cell. HIV then forces the cell to make many more copies of the virus. To make these copies, the cell uses proteins called enzymes. When the activity of these enzymes is reduced, the production of HIV slows to a very low level.

All three medicines in Triumeq interfere with enzymes needed by HIV, including an enzyme called reverse transcriptase and another one called integrase. These enzymes are used by HIV-infected cells to make more copies of HIV.

Since the drugs in Triumeq inhibit, or reduce, the activity of these enzymes, Triumeq causes HIV-infected cells to slow down or stop producing new viruses.

How do people with HIV use Triumeq?

Triumeq is a combination of three anti-HIV drugs. Such combinations are called antiretroviral therapy, or ART. For more information on ART, see CATIE's *Your Guide to HIV Treatment*.

FACT SHEET

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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 Triumeq 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

1. Hypersensitivity testing

Before you first begin taking Triumeq, check with your doctor to find out if you have been screened for possible hypersensitivity to abacavir, one of the drugs in Triumeq. This screening is written as HLA-B*5701 and is done with a simple blood test. If you test positive for abacavir hypersensitivity then you cannot use Triumeq, or any other medicine that contains abacavir such as these:

- Kivexa
- Ziagen
- Trizivir

If you test negative, then your risk of having a hypersensitivity reaction is greatly reduced. Speak to your doctor about your abacavir hypersensitivity results and whether it is safe for you to use Triumeq. For more information, see CATIE's fact sheet *Abacavir hypersensitivity screening*.

About hypersensitivity

In up to 8% of people with HIV who use abacavir, an exaggerated reaction against abacavir by the immune system—abacavir hypersensitivity—can occur. This reaction is very serious and can be fatal.

Although the hypersensitivity reaction can occur at any time while a person is taking abacavir, on average it occurs within the first six weeks of use. The manufacturer, ViiV Healthcare, states that you should stop using abacavir if you have signs or symptoms from two or more of the following groups:

- fever
- rash
- gastrointestinal symptoms (including nausea, vomiting, diarrhea or belly pain)
- general symptoms (including fatigue, lack of energy, achiness)
- respiratory symptoms (sore throat, shortness of breath, cough, unusual findings on X-rays of the chest)

If you develop symptoms from two or more of these groups while you are taking abacavir or any drug containing abacavir, you should stop taking this medicine and contact your doctor right away. If your doctor confirms that a hypersensitivity reaction to abacavir has indeed occurred, then abacavir should never be restarted, as a fatal reaction could occur within hours. You should also never take any other drug that contains abacavir.

2. Cardiovascular risk

Data from a well-designed trial (called Reprieve) of 7,769 people with HIV have been analysed. This was a study that recruited people at low to moderate risk of cardiovascular disease. Participants were randomly assigned to receive the cholesterol-lowering medicine pitavastatin or placebo. After an average of five years of monitoring, researchers found that people who received pitavastatin had a 35% reduced risk of major symptoms of cardiovascular disease (heart attack, stroke and so on).

Although people in Reprieve were not randomly assigned to receive their HIV treatment (they were all on treatment), the randomization used in the study helps to reduce the possibility of drawing biased conclusions when analyzing the data. The researchers are able to further analyse the information captured from the Reprieve study to answer important research questions. One such question is the potential risk associated with the use of the drug abacavir.

Since 2008, some observational studies have reported that there has been an increased risk of a heart attack in some people with HIV who used abacavir. However, because these studies were observational in design, they could not prove that use of abacavir was linked to an increased risk of a heart attack. Furthermore, most of these analyses from observational studies appeared to have issues – missing data or not being able to take into account factors such as smoking and substance use.

Now that has changed. An analysis from the very well-designed Reprieve study has found that recent or past use of abacavir was linked to a 50% increased risk for heart attack and other major symptoms of severe cardiovascular disease.

The analysis from Reprieve was able to consider factors such as sex, smoking, age, substance use, kidney health and so on. Even when the Reprieve researchers adjusted for these and other factors, abacavir was still linked to a significantly increased risk for heart attack and related issues.

These results from Reprieve have again heightened concern about the safety of abacavir-containing medicines.

Therefore, as a precaution, before starting Triumeq, let your doctor know if you have any of these or other risk factors for cardiovascular disease:

- your close family members (mother, father, brother, sister) have a history of problems such as heart attack or stroke
- you have high blood pressure, abnormal cholesterol or triglyceride levels in your blood, have pre-diabetes or kidney injury/disease.
- you use tobacco or smoke drugs

- you inject drugs or use stimulants (e.g. cocaine, crystal meth, MDMA/ecstasy, amphetamine or speed)

Your doctor can help you find ways to reduce your risk factors for cardiovascular disease. Your doctor can also help you decide if Triumeq is right for you.

3. Pregnancy

In May 2018, regulatory agencies issued cautionary statements because dolutegravir was associated with an apparent risk of birth defects in a clinical trial in the southern African country of Botswana. Specifically, HIV-positive women who used dolutegravir at the time of conception appeared to have a small but increased risk of giving birth to infants with a type of birth defect called a neural tube defect. This risk was greater than seen when women used other anti-HIV treatments.

However, long-term data have not shown an increased risk of birth defects associated with the use of dolutegravir-containing regimens outside of Botswana, including other African countries and in Canada. Furthermore, the number of children born with such birth defects in Botswana to women who used dolutegravir was limited. Also, over the course of several years in the same study, the risk of giving birth to an infant with a birth defect fell among women who used dolutegravir at the time of conception.

The good news is that the latest data from Botswana indicate the level of birth defects in infants born to women who use dolutegravir at the time of conception is now very low and similar to that seen in women who use other anti-HIV drugs at the time of conception.

If you are taking Triumeq and are pregnant or want to have a baby, let your doctor know.

4. Lactic acidosis and hepatic steatosis

Two related conditions, lactic acidosis (a build-up of lactic acid in the blood) and hepatic steatosis (excess fat in the liver), have historically occurred in some people who have used nucleoside analogues. These conditions can be serious or fatal. They have mostly been seen in women and people who are

overweight or who have been on nucleosides a long time, and can cause the following symptoms:

- nausea
- vomiting
- abdominal pain
- diarrhea
- unexpected tiredness
- unexpected muscle pain
- unexpectedly feeling cold, especially in the arms and legs
- feeling dizzy or light-headed

If any of these symptoms occur without apparent reason, call your nurse or doctor right away.

In the current era, lactic acidosis is very rare. If you do develop any of these symptoms, it does not necessarily mean you have lactic acidosis, but you should still let your doctor know right away.

5. Hepatitis B

If someone with hepatitis B infection is taking 3TC—a component of Triumeq—the hepatitis can grow worse or “flare up” if the medication is stopped. People who stop taking Triumeq should be carefully monitored. If you are co-infected with HBV, talk to your doctor about how best to treat this co-infection.

Side effects

1. General

Triumeq is usually well-tolerated. However, like many medicines, Triumeq can be associated with these symptoms:

- nausea
- vomiting
- diarrhea
- headache
- abdominal discomfort/pain

If these persist or are bothersome tell your doctor right away.

2. Weight gain

Some studies with HIV-positive people who used dolutegravir as part of combination treatment found that weight gain occurred. In some people the increased weight gain was modest—a few kilos—while in others it was more substantial. Research suggests that some HIV-positive people with the following features or characteristics tend to gain weight when on ART:

- women
- people of African, Black or Caribbean descent
- people whose CD4+ cell count fell below the 200 cell/mm³ level at some point in the past.

However, some HIV-positive people without these features can also gain weight. The cause of increased weight in HIV-positive people is not clear because studies suggest that HIV-negative people of the same age and gender are also generally gaining weight even though they are not taking ART.

An increase of one or two kilograms in weight over the course of one year is normal when initiating ART and is what has been reported in clinical trials in the current era. However, should you gain more than this amount of weight, speak to your nurse or doctor so that your weight gain can be assessed. Doctors and nurses also take into account a person's waist size and/or body mass index (BMI) – this is a number derived by dividing their height by the square of their weight. If your nurse or doctor has found that your BMI is increasing and is outside what is considered healthy then they will investigate possible causes for an increase in weight.

There may be one or more reasons that your BMI is increasing, including the following:

Physical activity – Are you getting enough daily physical activity, including walking and climbing stairs? If not, can you begin a program of exercise? Speak to your nurse or doctor about what kind of exercise is right for you.

Sleeping problems – Rest and sleep quality are sometimes overlooked aspects of health. A large

observational study in HIV-negative people found that people who have sleeping problems tend to gain weight. If you are unexpectedly gaining weight, speak to your doctor or nurse to rule out any sleep problems.

Emotional and mental health – Are there factors in your life that can affect how you respond to stressful events? For instance, when stressed, some people eat more fat and carbohydrate-rich foods as a source of comfort. Repeated engagement in excessive intake of carbohydrates and fatty foods can lead to weight gain over time. Depression can affect appetite—some people gain weight, others lose weight. If you notice weight gain along with changes in your mood, speak to your doctor or nurse.

Metabolic conditions, hormones and arthritis

Some conditions and life-stages are associated with weight gain, including the following:

- pre-diabetes and diabetes
- problems with the thyroid gland and its hormones
- being post-menopausal
- arthritis

Diet

Not everyone follows a diet that is informed by dietary guidelines. If you have access to subsidized dietary counselling (sometimes this is provided in large hospitals and clinics), you may benefit from consulting a registered dietitian. Registered dietitians can assess the quality and quantity of meals, and if necessary, provide helpful advice about making healthy changes.

Substance use

Alcohol contains calories. Is excess consumption of alcohol an issue for you? Excess consumption of alcoholic beverages could suggest unaddressed mental health and emotional issues.

Prescription medicines

Some prescription medicines (for conditions other than HIV) have the potential to cause changes in weight, particularly increased weight. It can be useful to speak to a pharmacist about all the medicines that you are taking to see if any are associated with changes in weight. You can then discuss any medicines that your pharmacist has identified with your doctor.

Bear in mind

While the above list covers some potential causes of weight gain in HIV-positive people, it is not exhaustive.

3. Emotional issues—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.

Symptoms of anxiety and depression can include the following:

- becoming easily upset or angry
- feeling fearful
- excessive worry
- unexpected feelings of sadness
- prolonged feelings of sadness, anger or depression

- feeling hopeless
- loss of pleasure in everyday activities
- unexpectedly feeling tired or a lack of energy
- difficulty falling asleep, staying asleep or waking up prematurely
- 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.

4. Older people

Triumeq has not been studied in large numbers of people aged 65 or older. Older people may have major organ systems (heart, liver, kidneys and so on) that do not work as well as in healthy younger people. Older people may also be taking multiple medicines that have the potential to interact with Triumeq. The manufacturer therefore advises doctors that in people aged 65 or older Triumeq should be used with caution.

5. Liver

The manufacturer (ViiV) states that patients who also have hepatitis B and/or C virus may be at increased risk for liver injury. ViiV recommends that doctors monitor the health of the liver in patients who take Triumeq.

6. 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.

Triumeq contains dolutegravir. This drug 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 Genvoya and Prezcobix.

However, the manufacturer recommends that Triumeq not be used by people whose kidneys are not functioning normally. That is, people whose eGFR (estimate glomerular filtration rate) is less than 50 mL/min should not use Triumeq.

Uncommon side effects

Side effects that were rare (less than 1%) in clinical trials included the following:

- feeling sleepy in the day time
- muscle weakness
- muscle pain

Drug interactions

In general, integrase inhibitors such as dolutegravir (one of the drugs in Triumeq) 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. Below are some drug interactions; this list is not exhaustive. Always speak to your pharmacist and doctor about your HIV treatment and its potential for interactions with other medicines and/or herbs or supplements that you are taking.

The manufacturer has not specifically conducted drug interaction studies with Triumeq. It has instead done drug interaction studies with a combination of the drugs used in Triumeq (dolutegravir + abacavir + 3TC).

Here are recommendations from the manufacturer about potentially significant drug interactions with dolutegravir (in Triumeq):

Other HIV drugs

Etravirine (Intelence) – 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 (Norvir)
- 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
- Roloids
- Tums

Viiv's advice for supplements containing iron and/or calcium is as follows:

"When taken with food, Triumeq and calcium and/or iron supplements or multivitamins containing calcium and/or iron can be taken at the same time." If you are taking Triumeq on an empty stomach, it "should be taken two hours before or six hours after taking supplements containing calcium and/or iron."

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 should be used at a dose of 50 mg twice daily 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.

Here are recommendations from the manufacturer about potentially significant drug interactions with abacavir (in Triumeq):

- Methadone – for most people no adjustment to their dose of methadone is needed.

- Alcohol – although drinking alcohol can increase the concentration of abacavir in the blood, this is not considered clinically meaningful.

These additional drugs should not be taken by someone using Trimeq – abacavir (Ziagen), Combivir, and Trizivir.

Here are recommendations from the manufacturer about potentially significant drug interactions with 3TC (in Trimeq):

FTC (emtricitabine, Emtriva and in Hepsera, Truvada, Complera, Stribild and Atripla) – these drugs should not be taken by Trimeq users.

Multiple sclerosis (MS) treatments

Viiv recommends that Trimeq not be used in people who are taking the drug fampridine (also known as dalfampridine) as Trimeq may cause increased concentrations of this drug in the body, leading to side effects.

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. Trimeq is a complete treatment in one pill.

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 medicines 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 can 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.

Dosage

Trimeq is available as a purple film-coated tablet. It contains the following drugs:

- dolutegravir – 50 mg
- abacavir – 600 mg
- 3TC – 300 mg

Trimeq is approved for use by adults 18 years of age or older. It is a complete regimen in one pill. It is meant to be taken once daily, day or night, without food or water restrictions.

If you miss a dose, the manufacturer recommends that you take it “as soon as you remember, but if your next dose is due within four hours, skip the dose you missed and take your next one at the usual time. Then continue your treatment as before.”

If you continue to miss doses, speak to your doctor, nurse or pharmacist about ways of helping you stick to a regular schedule of pill-taking.

Availability

Trimeq is licensed in Canada for the treatment of HIV infection in adults. Your doctor or pharmacist can tell you more about the availability and coverage of Trimeq in your region. CATIE's online module *Federal, Provincial and Territorial Drug Access Programs* also contains information about Canadian drug coverage.

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