

Complera

Summary

Complera is the name of a fixed-dose co-formulation of three anti-HIV drugs: tenofovir, FTC and rilpivirine. Complera can be used by itself as combination therapy for people with HIV who have not taken anti-HIV drugs in the past and who have HIV that is not resistant to any of the drugs in Complera. General side effects of Complera include headache and sleep problems. Complera is taken once daily with a meal.

What is Complera?

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

- Rilpivirine (Edurant), which belongs to a class of drugs called non-nukes or NNRTIs
- Tenofovir DF (Viread), which belongs to a class of drugs called nucleotide analogues
- FTC (emtricitabine, Emtriva), which belongs to a class of drugs called nucleoside analogues, or nukes

Because Complera contains these three medications, it can be used as a once-daily treatment for HIV infection (see *How do people with HIV use Complera?*).

How does Complera 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.

All three medicines in Complera interfere with an enzyme called reverse transcriptase, which is used by HIV-infected cells to make more HIV. Since Complera inhibits, or reduces, the activity of this enzyme, this drug causes HIV-infected cells to greatly slow down producing new viruses.

How do people with HIV use Complera?

Because it contains three anti-HIV drugs, Complera is considered antiretroviral therapy, or ART. For more information on ART, see CATIE's *Your Guide to HIV Treatment*.

FACT SHEET

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Complera is a complete treatment in one pill and is meant to be used by HIV-positive adults who:

- do not have HIV that is resistant to tenofovir, FTC and related drugs (these are commonly called nucleoside analogues or nukes);
- do not have HIV that is resistant to rilpivirine and related drugs such as nevirapine, efavirenz (in Atripla) and so on; and
- have levels of HIV in the blood (viral load) less than 100,000 copies/mL

Complera is taken once daily with a meal. Complera needs the fat in a meal to help ensure it is absorbed.

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 Complera nor any other anti-HIV medication is a cure for HIV. It is therefore important that you see your doctor for check ups 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. 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

Most people who are prescribed Complera will experience few or no problems, but some issues to be aware of include the following:

1. Mental health

In clinical trials, problems related to depressive illness occurred in some people who used rilpivirine-containing regimens, including Complera.

Symptoms included depression, anxiety and negative thoughts. In about 5% of participants, the severity of these symptoms ranged from moderate to life-threatening.

However, only about 1% of Complera users in clinical trials needed to stop taking this drug because of symptoms of depressive illness. Mental health issues are relatively common in HIV infection (regardless of whether or not people are taking treatment or the type of treatment).

Some people who use Complera may experience problems with thoughts and feelings. For example, you may have one or more of the following:

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

If you notice any of these problems before or after you have started to take Complera, talk to your doctor right away.

2. Cardiovascular health

The manufacturer advises that Complera should be used with caution in people who might have cardiovascular health conditions, including abnormal heart rhythms, heart failure, poor circulation of blood to the heart and so on. In clinical trials, researchers found that exposure to rilpivirine (one of the drugs in Complera) gradually affected the hearts of some volunteers

so that they were more likely to develop abnormal heart rhythms.

Symptoms of abnormal heart rhythms can include the following:

- dizziness
- fainting
- heart palpitations (a feeling that your heart is pumping very hard or fast when you are at rest)
- seizures

If you develop any of these symptoms, talk to your doctor right away.

If you have cardiovascular disease, including abnormal heart rhythms, or have a parent, brother or sister with any type of heart problem, let your doctor(s) know.

3. Hepatitis and liver health

Rilpivirine (one of the drugs in Complera) has been tested in only a small number of people with mild-to-moderate liver injury. Therefore, the manufacturer recommends that people with severe liver injury do not use Complera and that it be used with caution in people with mild-to-moderate liver injury.

In some clinical trials in which HIV-positive patients who are co-infected with hepatitis B or C received rilpivirine, increased levels of liver enzymes in the blood were found. The increased levels of these enzymes were greater than in other clinical trial participants who were not co-infected with hepatitis viruses.

The manufacturer recommends lab testing of blood before starting and during therapy with Complera. These tests should include screening for any liver injury or disease.

Increased levels of liver enzymes may suggest liver inflammation, liver injury and dysfunction; talk to your doctor about your test results.

4. Pancreatitis

There have been reports of painfully swollen pancreas glands in some people taking tenofovir (one of the drugs in Complera) as part of ART. Higher-than-normal levels in the blood of the enzyme amylase (made by the pancreas) have been detected in people taking tenofovir. This increase may suggest inflammation in the pancreas. Symptoms of pancreatitis can include the following:

- abdominal pain, particularly when laying down
- nausea
- vomiting
- unexpected sweating
- fever
- anxiety

If any of these symptoms occur, talk to your doctor right away.

5. Pregnancy

As there is no information from large numbers of pregnant women on the safety of Complera for these women or their fetuses, the manufacturer recommends that Complera “should not be used during pregnancy unless the benefits outweigh the potential risks to the fetus.”

6. Age

The manufacturer recommends that Complera should be used with caution in patients 65 years and older since clinical trials did not enroll sufficient people in this age group to assess its safety.

Side effects

The following is not a complete list of potential side effects; speak to your pharmacist and doctor to find out more. In some cases, researchers are not certain why some side effects occur.

1. General

Information from clinical trials suggest that Complera is generally well tolerated.

Here is a list of some symptoms reported by rilpivirine users in clinical trials; usually these side effects were mild and temporary:

- dizziness
- feeling sleepy during the daytime
- headache
- rash
- nausea
- stomach pain

If these or other symptoms persist or are bothersome, let your doctor know.

2. Depression (see Warnings)

Complera has the potential to cause depression and anxiety, although in clinical trials, less than 10% of people reported this problem. Before severe depression occurs subtle symptoms, which may possibly be related may appear, including:

- difficulty concentrating
- problems falling asleep
- problems staying asleep
- not feeling refreshed after a night's sleep
- worrying excessively
- persistent irritability
- difficulty remembering
- unexpected fatigue
- changes in appetite
- persistent nightmares

If you notice any of these symptoms or changes to your mood, speak to your doctor right away.

3. Lactic acidosis

In very rare cases, people who have used the medicines in Complera have experienced a condition called lactic acidosis—higher-than-normal levels of lactic acid in the blood. Researchers are not sure why this happens. Women who are overweight

are at increased risk for lactic acidosis. Sometimes the liver of a person with lactic acidosis becomes swollen because of fatty deposits.

Signs and symptoms of lactic acidosis may include the following:

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

If these symptoms persist, see your doctor right away.

4. Bone health

Complera contains tenofovir DF. This drug is associated with gradually thinning bones in some people with HIV. Before you start taking Complera, tell your doctor if you have bone problems, thinner-than-normal bones (osteopenia or osteoporosis), if you have had broken bones in the past, or if your parents, brothers or sisters have bone problems.

In clinical trials of regimens containing tenofovir, thinner bones in the spine and elsewhere, as well as bone pain have been reported. Thinner bones are generally weaker and are at increased risk for breaking (fractures) should accidents or trauma occur.

Researchers are not certain why bone thinning may occur in some people exposed to tenofovir. One theory is that bones became thinner because tenofovir DF may have caused the kidneys to malfunction. The kidneys filter blood, putting waste materials into the urine and returning nutrients back to the blood. In the cases of tenofovir-associated bone loss, damaged kidneys may not be able to restore bone-building nutrients to the blood.

Bear in mind that some people with HIV can develop thinner-than-normal bones without ever

using tenofovir DF or any other medicines. Studies have found that after starting ART, some people may have their bone density decrease. The decrease in bone density tends to stabilize within one or two years after starting ART. It may be useful for you to discuss with your doctor the possibility of having bone density assessments done before you begin taking Complera or any other anti-HIV therapy. If your bones are thin, talk to your doctor about your intake of calcium and vitamin D₃. Regular monitoring of bone density may also be useful for some people.

For more information about vitamin D and bones, see CATIE's *A Practical Guide to a Healthy Body for People Living with HIV* and *A Practical Guide to HIV Drug Side Effects*.

5. Kidney health

Complera contains tenofovir DF, which is broken down by the kidneys. There have been reports of kidney dysfunction in some people who used tenofovir. The manufacturer recommends that doctors screen patients for kidney problems prior to initiating therapy with Complera. Having regular blood and urine tests done while you are taking Complera can help your doctor assess your kidney health. Some of the tests used to assess kidney health include the following:

- creatinine
- e-GFR (estimated glomerular filtration rate)
- calcium
- phosphorus
- bicarbonate

In addition to tenofovir, there are other medications processed by the kidneys that have the potential to injure these organs. Many of these medications are antibiotics, such as:

- beta-lactams—penicillin and amoxicillin
- quinolones—ciprofloxacin and related compounds
- aminoglycosides—amikacin and gentamicin
- macrolides—erythromycin

- tetracyclines—minocycline
- anti-tuberculosis agents—rifampin and ethambutol
- other antibiotics—co-trimoxazole (Septra/Bactrim) and vancomycin (Vanocin)

Bear in mind that there are other medications that can potentially damage the kidneys, including:

- antiviral agents—acyclovir (Zovirax), valacyclovir (Valtrex), cidofovir (Vistide), foscarnet (Foscavir), indinavir (Crixivan)
- antifungal agents—amphotericin B (Fungizone), intravenous pentamidine
- anti-seizure drugs—phenytoin, carbamazepine, valproic acid
- drugs used to relieve pain and/or inflammation—acetaminophen (Tylenol), ibuprofen (Advil, Motrin), indomethacin (Indocid), naproxen (Naprosyn)
- transplant drugs—cyclosporine (Neoral, Sandimmune)

The above list is not exhaustive – speak to your pharmacist to find out more.

6. Changes in body shape

In general, Complera does not cause significant changes in body shape. However, people who initiate ART generally experience a degree of weight gain (usually a few pounds or kilos) in subsequent months or years. This occurs because ART helps to improve overall health and the health of the digestive tract in particular.

Food interactions

Complera must always be taken with a meal so that it is absorbed.

Avoid eating grapefruit or drinking grapefruit juice as these will increase the concentration of rilpivirine in your body leading to side effects.

Drug and herb interactions

Always consult your doctor and pharmacist about taking any other prescription or non-prescription medication, including over-the-counter medicines, herbs, supplements and street drugs.

Some drugs can interact with Complera, increasing or decreasing the levels of the medicines in Complera in your body. Increased drug levels can cause you to experience side effects or make pre-existing side effects worse. On the other hand, if drug levels become too low, HIV can become drug-resistant and your future treatment options may be reduced.

If you must take a drug that has the potential to interact with your other medications, your doctor can do the following:

- adjust the dose of either your anti-HIV drugs or other medications; or
- prescribe different anti-HIV drugs.

The manufacturer warns that the following drugs and herbs should not be used with Complera because they can *severely* reduce the concentration of rilpivirine (one of the drugs in Complera) in the blood and cause HIV to become resistant to rilpivirine and other anti-HIV medications (note that the following list is not exhaustive):

- antibiotics for tuberculosis or MAC (mycobacterium avium complex) – rifabutin (Mycobutin), rifampin (Rifadin, Rofact and in Rifater), rifampicin and rifapentene
- antiseizure drugs – carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- corticosteroids – dexamethasone given as pills or by injection. High doses of corticosteroids can accumulate in the body and interact with rilpivirine
- herbs – St. John’s wort (hypericin, hyperforin)
- proton pump inhibitors – dexlansoprazole (Dexilant), esomeprazole (Nexium), lansoprazole (Prevacid), omeprazole (Losec), pantoprazole (Pantoloc), rabeprazole (Pariet)

The manufacturer warns that the following drugs should not be used with Complera because they

can greatly *increase* levels of rilpivirine (one of the drugs in Complera) and can cause side effects:

- non-nukes – efavirenz (Sustiva, also in Atripla), etravirine (Intelence), nevirapine (Viramune) and delavirdine (Rescriptor)

The manufacturer warns that the following drugs can *increase* rilpivirine levels and suggests that physicians exercise caution when prescribing these drugs to patients who are taking Complera:

- antacids containing aluminum, magnesium hydroxide or calcium carbonate. These drugs should be used with caution as they can affect the acidity of the stomach and greatly decrease absorption of rilpivirine and reduce its levels in the blood. The manufacturer recommends that antacids should only be used “either at least two hours before or at least four hours after Complera.”
- antifungal agents – fluconazole (Diflucan), ketoconazole, itraconazole (Sporanox), posaconazole (Spirafil) and voriconazole (Vfend). These can all *increase* levels of rilpivirine in the blood and rilpivirine can *reduce* the concentration of these drugs, which can lead to new or recurring fungal infections
- HIV protease inhibitors – atazanavir (Reyataz), darunavir (Prezista), fosamprenavir (Telzir), lopinavir-ritonavir (Kaletra), ritonavir (Norvir), saquinavir (Fortovase), tipranavir (Aptivus). Rilpivirine should not increase levels of these other drugs
- macrolide antibiotics – clarithromycin (Biaxin), erythromycin and troleandomycin can all *increase* rilpivirine levels and lead to side effects. The manufacturer suggests that where possible, physicians consider the use of an alternative macrolide, such as azithromycin (Zithromax)

The following drugs can *decrease* rilpivirine levels and must be used with caution:

- histamine₂-receptor antagonists – cimetidine (Tagamet), famotidine (Pepcid), nizatidine, ranitidine (Zantac). These drugs reduce the acidity of the stomach and can therefore significantly reduce the absorption of rilpivirine.

This can lead to HIV becoming resistant to rilpivirine and other anti-HIV drugs. The manufacturer suggests that these drugs should be used with caution and if they must be used, they should only be taken “at least 12 hours before or at least four hours after Complera.”

Hepatitis C treatment

Treatments for HCV such as Harvoni (ledipasvir + sofosbuvir) can raise levels of tenofovir DF in the blood. The manufacturer recommends that doctors monitor Complera users who take Harvoni for side effects related to tenofovir DF.

Complera may interact with other treatments for hepatitis C; speak to your doctor/nurse and pharmacist to find out more.

Other drugs

Medicines that cause people to urinate excessively (such as water pills or diuretics) or have diarrhea (laxatives or enemas), or other drugs such as amphotericin B (Fungizone, Abelcet) can upset the balance of minerals in your blood and could affect your heart’s rhythm. The manufacturer recommends that such drugs be used with caution in people taking Complera.

Interactions are *not* expected

The manufacturer does not expect Complera to interact with these drugs:

- methadone
- HIV and hepatitis drugs – receptor blockers (maraviroc, Celsentri) and nukes for hepatitis C treatment, such as ribavirin; integrase inhibitors, such as raltegravir (Isentress). The drug ddl (Videx) needs to be taken on an empty stomach at least two hours before or at least four hours after taking Complera
- erectile dysfunction drugs, such as sildenafil (Viagra), tadalafil (Cialis) or vardenafil (Levitra)

- lipid-lowering agents, called statins, including atorvastatin (Lipitor), rosuvastatin (Crestor) and similar drugs
- oral contraceptives (“the pill”)

Resistance, cross-resistance and treatment interruption

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes are called mutations and can cause HIV to resist the effects of anti-HIV drugs, which means those drugs will no longer work for you. Combining rilpivirine with at least two other anti-HIV drugs, as Complera does, 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. If doses are delayed, missed or not taken as prescribed, blood levels of the drugs in Complera may fall too low. If this happens, resistant virus can develop. If you are having problems taking your medications as directed, speak to your doctor and nurse 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 options might be, your doctor can have a small sample of your blood analyzed using resistance testing. Should HIV in your body become resistant to rilpivirine, your doctor can recommend a new drug combination for you.

Dosage and formulations

Complera is available as purplish-pink tablets. Each tablet contains the following medications:

- rilpivirine—25 mg
- FTC—200 mg
- Tenofovir DF—300 mg

The adult dose is one tablet taken once daily with a meal.

Availability

Complera is licensed in Canada for the treatment of HIV infection in adults who have never used antiretroviral drugs. Your doctor can tell you more about the availability and coverage of Complera 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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Disclaimer

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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