Efavirenz, didanosine, lamivudine

Efavirenz/ddI/3TC is a combination of three drugs recommended by the World Health Organisation for the treatment of HIV infection. Both ddI and 3TC belong to the nucleoside analogue class of antiretroviral drugs. Efavirenz is a non-nucleoside reverse transcriptase inhibitor.

Efavirenz/ddI/3TC is a once-a-day combination available as a kit, the Odivir kit, which contains all three medications efavirenz, ddI (enteric coated) and 3TC.
Information on starting treatment with efavirenz + didanosine (ddI) + lamivudine (3TC)

Supplied as Odivir Kit, fixed dose quantities of each drug in strips for easier daily dosing

Information on starting treatment with

Dosage:

- Efavirenz: 600mg once a day
- Didanosine EC (ddI): 400mg for patients weighing over 60kg, 250mg for those under 60kg, once a day
- Lamivudine (3TC): 150mg twice daily.

The Odivir kit is not suitable for people weighing with renal insufficiency or for those who require lower doses due to adverse events

Administration:

- Once daily*: One pill each efavirenz, didanosine and lamivudine. Pills should be taken on an empty stomach at least two hours after a meal and at night, preferably taken before bedtime to reduce the incidence of side effects during waking hours
- *Daily doses should be taken as close to 24 hours apart as possible.
- DdI tablets should not be split in half, crushed or dissolved in water; this will damage the contents and make the drug less effective.
Odivir Kit

- Odivir KIT 250 contains 250mg of ddI for people weighing less than 60kg
- Odivir KIT 400 contains 400mg of ddI for people weighing more than 60kg
- Odivir KIT is not suitable for:
  - Patients weighing less than 50kg (7 ½ stone)
    (due to need for lower 3TC dose)
  - Patients with renal insufficiency

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Efavirenz and central nervous system

**Side effects:** The combination of efavirenz/ddI/3TC is generally well tolerated in most patients, nevertheless, health care workers should be on the look out for the following adverse events. Some of these side effects can be managed with palliative therapy, but others may require dose adjustments, temporary or permanent discontinuation of treatment.

**Central Nervous System effects:** Possibly half of patients on efavirenz experience some neurological side effects ranging from altered senses, dizziness, headache, insomnia, depression, impaired concentration, agitation, nightmares, and drowsiness. Some of these symptoms may be manageable by taking the drug before bedtime. These side effects begin within days of starting efavirenz treatment, and will lessen after a few months on treatment in the majority of cases (approx 10% may complain of longer-term problems). A minority of patients experience severe psychiatric symptoms including delusions, manic episodes and severe depression. Such severe side effects may require treatment discontinuation as patients may even become suicidal and require anti-psychotic medication. This is particularly common in people with a history of mental illness or recreational drug use.

**Temporary Nucleoside-Related Side Effects:** Soon after starting treatment, patients may experience headache, insomnia, fatigue and gastrointestinal upset (nausea, vomiting, and diarrhoea)—but these side effects are generally transient. Patients may be given medications to manage these side effects.
Other side effects

**Pancreatitis.** All three drugs, especially didanosine, have been associated with pancreatitis, inflammation of the pancreas, which can be fatal. Symptoms include nausea, vomiting and abdominal pain. Blood tests may find elevated levels of pancreatic enzymes. The incidence may be dose related, underscoring the need to dose ddI properly by body weight, and it is increased in patients who have had pancreatitis or gallstones in the past. Other risk factors include alcohol and obesity. Treatment should be discontinued if pancreatitis is suspected, and if it is confirmed patients should be switched to a regimen that does not include ddI.

**Lactic acidosis:** Prolonged NRTI use can lead to the accumulation of dangerously high levels of lactic acid in the bloodstream. Lactic acidosis is a very rare syndrome, but if it goes unrecognised, mortality is high. It is more common in women, those with high body mass, and, possibly, pregnancy. Patients experiencing it may complain of weakness, abdominal pain, nausea and vomiting, shortness of breath, fatigue and hypotension. The initial symptoms are variable; an early clinical syndrome may include generalized fatigue and weakness. These may observed as soon as one month or as late as 20 months after starting therapy. All drugs should be stopped at once because the longer a patient is on therapy the more symptoms worsen.
Other side effects

Rash and liver toxicity can occur on either nevirapine or efavirenz. Rash and liver toxicity is generally less severe on efavirenz. Cases of hypersensitivity reaction, a life-threatening syndrome of rash, fever, abdominal pain, diarrhea, dry cough and jaundice, have been reported in only a few patients on efavirenz. It seems that efavirenz and nevirapine do not cause these allergic toxicities in the same manner. Patients who experience rash or liver toxicity on efavirenz can probably be safely switched to nevirapine if possible. Nevertheless, monitor such patients closely.

Less common side effects on efavirenz include alcohol intolerance, fever, aches, pain and fatigue, fluid retention (in the hands and feet), dry mouth, elevated lipids, asthma, and changes in vision and taste.

Peripheral neuropathy is damage to the peripheral nervous system. The symptoms range from tingling, or burning sensations to severe pain usually in the feet, legs and sometime in the arms and hands. Numbness and muscle weakness can also occur. Peripheral neuropathy has been reported in 6-15% of patients taking didanosine, but has not been reported in studies of this particular combination. Peripheral neuropathy may be more common (and severe) in patients taking other neurotoxic drugs. Symptoms usually resolve within a few weeks of stopping treatment.

Neutropenia: On rare occasions, lamivudine may cause neutropenia (a drop in the levels of a type of blood cell that fights bacterial infections).

Lipoatrophy: A longer-term side effect of antiretroviral treatment can be lipodystrophy, an abnormal change in body fat distribution. Reports suggest that part of the syndrome, lipoatrophy, the loss of fat from under the skin, may be associated with nucleoside analogue treatment. The fat loss is most obvious in the arms, legs, buttocks and face. The syndrome can result in facial wasting, shrunked buttocks and prominent veins on the arms and legs and may require dose reduction or discontinuation of nucleoside analogues.

Occasional, needs ongoing monitoring

- Neutropenia
- Peripheral neuropathy
  - nerve damage in feet and legs – burning pain – rare with this combination but can be caused by ddI.

Mild

- Rash in first weeks
  - If severe rash or hepatitis, switch to nevirapine (not caused by the same mechanism, so safe to do this)

Possible, long-term

- Fat loss from limbs and face (lipoatrophy)
Hyperuricemia: Didanosine has been associated with asymptomatic hyperuricemia; treatment suspension may be necessary if clinical measures aimed at reducing uric acid levels fail.

Interrupting Treatment: Whenever treatment is interrupted, for whatever reason, all drugs should be stopped at once to prevent the development of resistance.

Lamivudine has a suppressive effect on the hepatitis B virus. In clinical trials, some patients with HIV and chronic hepatitis B virus co-infection have experienced clinical or laboratory evidence of recurrent hepatitis upon discontinuation of lamivudine-containing regimens. Consequences may be particularly severe in such patients who are discontinuing therapy due to liver toxicity.
Drug interactions

**Drug interactions:** Efavirenz should not be taken with clarithromycin, terfenadine, astemizole, cisapride, triazolam and midazolam.

Efavirenz may reduce methadone levels in the body and lead to withdrawal symptoms. If such symptoms occur, the methadone dose may be increased by 10mg per dose until symptoms disappear.

Patients on foscarnet or ganciclovir should not take 3TC-containing regimens.

Because of the risk of pancreatitis and neuropathy on didanosine, drugs that may cause pancreatic toxicity or increase the risk of pancreatitis or neuropathy should only be used only with extreme caution. These include rifampicin, ganciclovir, alpha interferon, H2 blockers and omeprazole.

Tetracycline antibiotics and intravenous pentamidine should not be used with didanosine.
Efavirenz and pregnancy

**Contraception:** Efavirenz/ddI/3TC does not reduce the effectiveness of oral contraceptives. Because of the risk of birth defects, women who wish to avoid pregnancy should either not use efavirenz-containing regimens or they should use birth control.

**Pregnancy:** DO NOT USE efavirenz/ddI/3TC in women who desire or may become pregnant. DO NOT START efavirenz without a pregnancy test. Efavirenz caused significant birth defects in primates exposed to it in utero, and to at least one human infant who was accidentally exposed to the drug in utero. Efavirenz is particularly dangerous during the first trimester, so pregnancy should be avoided by women taking the drug. Women who may become pregnant while on efavirenz should be advised of the danger of birth defects and be switched to a different drug, if possible.
Test questions

1. What are the doses of each drug and when should they be taken?
   - Answer

2. What are the instructions regarding food with this combination?
   - Answer

3. What are the possible side effects?
   - Answer

4. What drugs should not be taken alongside efavirenz?
   - Answer

5. What do women who are pregnant or likely to become pregnant need to know about efavirenz?
   - Answer

For more information see individual drug entries at www.aidsmap.com