Efavirenz, zidovudine, lamivudine
Information on starting treatment with Efavirenz/AZT/3TC

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

The combination of efavirenz/AZT/3TC is available as:

Efavirenz (trade names Stocrin (made by MSD), Efavir (Cipla), Estiva (Genixpharma), Viranz (Aurobindo/Imunus), Aviranz (Ranbaxy)

A tablet combining AZT and 3TC at fixed doses:

- Combivir (made by Glaxo Smith Kline) contains zidovudine (AZT) and lamivudine (3TC)
- Duovir (Cipla) contains zidovudine (AZT) and lamivudine (3TC)
- Zidolam (Genixpharma) contains zidovudine (AZT) and lamivudine (3TC)
- Zidovex-L (Aurobindo/Imunus) contains zidovudine (AZT) and lamivudine (3TC)

Virocomb (Ranbaxy) contains zidovudine (AZT) and lamivudine (3TC)
Dosing schedule

Efavirenz: 600mg once a day either as three 200mg capsules or one 600mg tablet

Zidovudine (AZT): 300mg bid twice daily. Patients with impaired kidney function or who require dosage adjustment due to toxicity cannot use a fixed dose tablet combining AZT and 3TC

Lamivudine (3TC): 150mg twice daily.

The fixed dose AZT/3TC tablet is not suitable for people weighing less than 50kg, for those with renal insufficiency or for those who require lower AZT doses due to adverse events.

*Once daily doses should be taken as close to 24 hours apart as possible; twice-daily doses should be taken as close to 12 hours apart as possible.

Side effects: The combination of efavirenz/AZT/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.
Efavirenz and central nervous system

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.

Patients should be warned to exercise care in driving or using machinery whilst experiencing central nervous system effects caused by efavirenz.

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: Both lamivudine and efavirenz have rarely 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.

Lactic acidosis: Prolonged NRTI use can lead to the accumulation of dangerously high levels of lactic acid in the blood stream. Lactic acidosis is a very rare syndrome, but if it goes unrecognised, the risk of death 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 generalised 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. The patient should be referred to a doctor if these symptoms develop.
Other side effects

**Neutropenia:** AZT, and less often 3TC, may cause neutropenia (loss of neutrophils which fight bacterial infections). If the absolute neutrophil count falls below 500/ml, switch from zidovudine to another nucleoside analogue or reduce the AZT dose (fixed dose AZT/3TC tablet should no longer be used). Neutropenia usually becomes evident after 6 to 8 weeks of treatment.

**Myopathy:** Muscle pain, inflammation, weakness and wasting occur in about 17% of patients on zidovudine with prolonged use of the drug. Weakness is especially pronounced around the hips, thighs and buttocks. If wasting becomes serious, a change to ddI or d4T may be necessary.

**Fat loss from limbs and face:** 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, shrunken buttocks and prominent veins on the arms and legs and may require dose reduction or discontinuation of nucleoside analogues.

**Anaemia:** AZT may cause anaemia (loss of oxygen-carrying red blood cells). The patient may appear pale, complain of tiredness and feel increasingly weak, without any signs of an infection. Patients with low haemoglobin levels prior to treatment are at risk of developing severe anaemia and should be monitored frequently where testing is available. Blood transfusion or zidovudine interruption may be necessary if it is not possible to switch from zidovudine to another nucleoside analogue (eg stavudine, didanosine or tenofovir). Anaemia may develop within 2 to 4 weeks of commencing AZT. Temporary dose reduction to 200mg is possible. Zidovudine dose reduction is not advisable as a long-term treatment strategy; sub-optimal dosing will lead to treatment failure and drug resistance.
Other side effects

**Mild problems – reassure that they are not serious**

- **Headache**
  - common in first weeks of efavirenz and ZDV treatment – use headache remedies, refer to doctor/district level if it lasts beyond first month
- **Nausea**
  - common in first weeks of ZDV treatment, may be reduced if taken with food
- **Fatigue**
  - common in first 4-6 weeks of ZDV treatment, refer to doctor/district level if it lasts longer
- **Blue/black nails**
  - quite common with ZDV not harmful, reassure
- **Rash in first weeks, caused by efavirenz**
  - seen in less than 5% of patients
- **If severe rash or hepatitis, switch to nevirapine**
  - not caused by the same mechanism, so safe to do this

**Minor side effects**

- which tend to pass after the first few weeks on this combination include headache (treat with painkillers or other available remedies and refer to doctor or district level if it persists beyond first month), nausea (take zidovudine with food to reduce nausea), fatigue (common in first 4-6 weeks of zidovudine treatment, but refer to doctor/district level if it persists) and blue/black nails (common not harmful).

**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, diarrhoea, 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.

**Interrupting Treatment:** Whenever treatment is interrupted, for whatever reason, all drugs should be discontinued 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.
AZT dose reduction

- If AZT dose reduction necessary, fixed dose AZT/3TC tablet must be stopped
  - Replace with:
    - 1 x 150mg 3TC twice daily
    - 1 X 200mg AZT twice daily
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 10 mg per dose until symptoms disappear.

Methadone may increase blood levels of zidovudine two-fold. Patients experiencing zidovudine-related adverse events may need dose reductions.

Alpha-interferon, ganciclovir, cancer chemotherapeutics co-trimoxazole and other drugs that have bone marrow effects may increase the likelihood of zidovudine’s hematologic toxicities in some patients with advanced HIV disease. Hematologic parameters should be monitored frequently in all patients receiving either of these combinations.

Phenytoin: Zidovudine may decrease phenytoin plasma levels.

Valproic Acid: Data suggest that valproic acid increases the oral bioavailability of zidovudine through inhibition of first pass hepatic metabolism. Patients should be monitored for a possible increase in zidovudine-related adverse events.

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

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

**Pregnancy:** DO NOT USE efavirenz/AZT/3TC in women who desire or may become pregnant. DO NOT BEGIN efavirenz treatment 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 daily doses of each drug (how many tablets and how often?)
   - Answer

2. What are the main side effects?
   - Answer

3. What action should be taken if the patient develops anaemia?
   - Answer

4. Which drug increases the risk of anaemia and neutropenia if taken alongside AZT?
   - Answer

5. Which drugs should not be taken alongside efavirenz?
   - Answer

6. 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