Efavirenz, stavudine and lamivudine

First line ART treatment for HIV infection

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

The combination of efavirenz, stavudine (d4T) and lamivudine (3TC) is available in the form of efavirenz tablets and a coformulated d4T/3TC tablet, or as separate stavudine and lamivudine tablets.
Dosing schedule

**Efavirenz**: 600mg (3 x 200mg capsules or one 600mg tablet) once a day (variously supplied as Stocrin (Merck Sharp and Dohme), Efavir (Cipla), Aviranz (Aurobindo/Imuno, Estiva (Hetero/Genixpharma) )

**Stavudine (d4T)**: 40mg or 30mg according to body weight (30mg if below 60kg) twice daily. *Remember to adjust dosage if patient gains or loses weight.* For patients with impaired kidney function, peripheral neuropathy, lipoatrophy, or weight < 50kg, the dose may need to be reduced to 15mg or 20mg twice daily (consult a specialist).

**Lamivudine (3TC)**: 150mg twice daily.

The fixed dose stavudine/lamivudine tablet is variously supplied as Lamivir-S (30 or 40mg) (Cipla), Lamistar 30 or 40 (Genixpharma).

The fixed dose stavudine/lamivudine tablet is not suitable for people weighing less than 50kg, for those with renal insufficiency or for those who require stavudine dose reductions to less than 30mg twice daily due to adverse events.
Administration:

**Twice a day:** One tablet each stavudine and lamivudine or one stavudine/lamivudine tablet

plus

**Once daily***: Three efavirenz 200mg capsules or one efavirenz 600mg capsule, preferably taken before bedtime to reduce the incidence of central nervous system side effects during waking hours

**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.**
Stavudine dosing by weight

- 40mg twice daily if >60kg
- 30mg twice daily if <60kg
- If the patient weighing less than 60kg gains weight, the stavudine dose will need to increase
- Renal insufficiency (impaired kidney function):
  - Do not use fixed dose stavudine/lamivudine capsule
  - Dose stavudine separately
  - Reduce stavudine to 20mg twice daily if >60kg
  - Reduce stavudine to 15mg twice daily if <60kg
Efavirenz and central nervous system

**Side effects:** The combination of efavirenz/stavudine/lamivudine is generally well tolerated in most patients, nevertheless, health care workers should be on the lookout for the following side effects. 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.

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

Peripheral neuropathy: Damage to the peripheral nervous system can be caused by both stavudine and lamivudine, but it is usually, or most commonly, due to stavudine. 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. This condition is dependent upon stavudine dose, duration of therapy and the use of other neurotoxic drugs. Symptoms usually resolve within 2-3 weeks after the discontinuation of d4T. d4T may then be re-started at a lower dose (20mg bid for patients > 60kg, 15mg bid for patients < 60kg) but use of the co-formulated tablet in such cases is no longer appropriate. If other drugs are available, substitution of another nucleoside analogue for stavudine may be preferable.
Other side-effects

Occasional but life threatening
- Pancreatitis
  - Sharp pain below stomach, nausea, vomiting, fever
  - Very rare with these drugs – linked to stavudine and lamivudine
- Lactic acidosis
  - Rare, linked to zidovudine or stavudine
  - Fatigue, abdominal pain, nausea and vomiting, muscle weakness and pain, weight loss, breathing difficulty. Refer to doctor/district hospital.
  - Stop treatment and use bicarbonate, fluid, breathing support
  - Refer to district hospital level to resume treatment, switch from zidovudine to tenofovir if available

Occasional, needs ongoing monitoring
- Neutropenia

Pancreatitis: All three drugs in this regimen have rarely been associated with pancreatitis, inflammation of the pancreas, primarily in children with advanced disease. Pancreatitis can be fatal. Symptoms include nausea, vomiting and abdominal pain. Blood tests may find elevated levels of pancreatic enzymes.

Lactic acidosis: Prolonged NRTI use (in particular stavudine) 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 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. The longer a patient is on therapy the more symptoms worsen. If symptoms develop, the patient should be referred to a doctor/district hospital.

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

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, in particular d4T. 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 d4T.

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 with food to reduce nausea).

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.
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.

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

**Contraception:** Efavirenz/d4T/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 additional barrier methods of birth control.

**Pregnancy:** DO NOT USE efavirenz/d4T/3TC in women who desire or who may become pregnant. Efavirenz caused significant birth defects in monkeys exposed to it in the womb, and to at least one human infant who was accidentally exposed to the drug in the womb. Efavirenz is particularly harmful 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 peripheral neuropathy?
   - 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