Nevirapine/stavudine/lamivudine is a combination of three drugs recommended by the World Health Organisation for the treatment of HIV infection.

Each drug in this combination is dosed as a separate tablet.
Nevirapine, stavudine and lamivudine (non-fixed dose)

Lead in dosing for the first 14 days

- Nevirapine must be given at a lower dose (one tablet per day)
- Treatment must never start at full dose
- Increased risk of serious rash and life threatening reaction if NVP used at full dose in first 14 days
- The patient must receive the stavudine tablet that is suitable for their weight

Dosage:

**Nevirapine:** 200mg once a day (for the first two weeks*); afterwards 200 mg twice a day

**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 or peripheral neuropathy, the dose may need to be reduced to 15mg or 20mg twice daily (consult an HIV specialist)

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

Baseline tests:

If possible, conduct liver function tests prior to starting lead-in nevirapine/d4T/3TC therapy and at appropriate intervals during therapy. Do not use nevirapine-based therapy in patients with greater than moderate ALT or AST abnormalities.
Nevirapine 200mg (1 tablet per day)  
+  
Correct stavudine dose for patient’s weight (30 or 40mg twice daily)  
+  
Lamivudine 150mg twice daily  

Administration:  
First two weeks*:  
- Twice daily**:  
  One pill stavudine (30 or 40mg depending on patient’s weight)  
- One pill of lamivudine (150mg)  
  plus  
- Once daily:  
  One nevirapine pill (200mg)  

*If rashes of moderate or worse severity develop within the first 14 days of lead-in, do not increase nevirapine dose or start using the fixed dose three drug tablet until the rash has resolved.  
**Twice daily doses should be taken as close to 12 hours apart as possible.
Nevirapine, stavudine and lamivudine (non-fixed dose)

Dosing from day 14

- Do not switch until serious rash has improved
- Increase nevirapine dose to one tablet TWICE daily
- The patient must receive the stavudine tablet that is suitable for their weight

Administration:

After two weeks (or rash has resolved):

Increase nevirapine dose to one tablet (200mg) twice daily.

**Twice daily doses should be taken as close to 12 hours apart as possible.

Nevirapine dosing: special notes

Nevirapine must be introduced at half dose for 14 days to reduce the risk of serious rash.
Stavudine dosing by weight

- 40mg stavudine content tablets if over 60kg weight
- 30mg stavudine content tablets if under 60kg weight

Dose adjustment

- If the patient weighing less than 60kg gains weight, the stavudine dose may need to increase
- If the patient develops peripheral neuropathy, treatment needs to be adjusted.
- Tablets containing 30 or 40mg of stavudine are not suitable for people with renal insufficiency; these patients need to receive a dose of 15mg or 20mg twice daily depending on body weight.

Stavudine dosing: special notes

A stavudine tablet containing 40mg of stavudine should be given to patients weighing over 60kg twice daily.

A stavudine tablet containing 30mg of stavudine should be given to patients weighing less than 60kg twice daily.
Nevirapine side effects and monitoring

- Rash and hepatitis
  - Higher risk periods:
    - Rash: first month,
    - Hepatitis: first six months
  - Rash appears on arms and torso, severe in up to 10%

- Stevens-Johnson syndrome: severe skin eruption, peeling, fluid loss. Stop treatment immediately and refer to district hospital. When treatment resumes, use efavirenz instead of nevirapine.

- Rash and/or hepatitis may also be caused by isoniazid and rash by cotrimoxazole

Side effects: The combination of nevirapine/d4T/3TC is usually 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.

- **Rash:** Nevirapine commonly causes a skin rash, though in some patients it can cause hepatitis and a life-threatening hypersensitivity reaction (see below). In developed countries, about 17% of the patients appear to develop a rash on nevirapine. The rash can be severe leading about 6-8% of patients to stop treatment. It may occur more often in women and in persons of Asian descent. The rash most commonly appears on the body and arms, usually within the first month of therapy, although occasionally it may start a few weeks later. Nevirapine should be stopped if the rash is severe or affects the mucous membranes, and is accompanied by fever and chills. If skin peeling occurs, hospital admission and fluid replacement treatment is recommended.

- **Isoniazid** can also cause these symptoms. Isoniazid toxicity usually occurs in the first two to three months of treatment with the drug, so it can be ruled out if a patient has already received treatment with isoniazid for several months.

- **Cotrimoxazole** can also cause rash, which usually occurs in the first two to three weeks after starting the drug, or after the immune system has begun to recover due to antiretroviral therapy.
**Hepatitis:** Nevirapine-associated liver toxicity (elevation in liver enzymes and hepatitis) can occur in about 13-17% of patients, and severe hepatitis may occur in 1-9%. It may be more common in patients with a history of alcohol abuse, co-infection with hepatitis B or C and in patients who are older or are women. Both lamivudine and stavudine may also contribute to liver toxicity. Monitoring of ALT and AST is strongly recommended, especially during the first six months of nevirapine treatment. If monitoring is not possible, symptoms that suggest liver toxicity are pain/tenderness in liver and abdomen area, yellowing of the whites of the eyes, pale stools, nausea and vomiting.

Treatment should be interrupted in patients experiencing moderate or severe ALT or AST abnormalities until these return to baseline values (see Interrupting Treatment below) or until symptoms go away. Nevirapine treatment should be stopped permanently if liver function abnormalities come back when treatment is resumed.
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 (e.g. isoniazid). 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). If other drugs are available, substitution of another nucleoside analogue for stavudine may be preferable.
Pancreatitis: Both stavudine and lamivudine has 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 because the longer a patient is on therapy the more symptoms worsen. Refer to a doctor/district level if these symptoms appear.

Neutropenia: On rare occasions, lamivudine may cause neutropenia (a drop in the levels of neutrophils, a type of blood cell that fights bacterial infections). The most frequent cause of neutropenia in patients taking this drug combination is likely to be concurrent treatment with cotrimoxazole.
Other side effects

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) and blue/black nails (common not harmful).

Lipoatrophy: A longer-term side effect of antiretroviral treatment can be lipodystrophy, an abnormal change in body fat distribution. This seems to be less common in regimens that use nevirapine as a cornerstone. However, 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.

Interrupting Treatment

Lamivudine has a suppressive effect on the hepatitis B virus. In clinical trials, some patients with HIV and chronic hepatitis B virus coinfection 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.

If treatment is interrupted for more than a week, restart with the lead-in dosing protocol (with one 200mg nevirapine tablet daily for the first 14 days in combination with d4T/3TC). If treatment was interrupted because of nevirapine-related side effects, watch for any signs of toxicity during lead-in treatment. Caution should be exercised before switching over to the three drug fixed dose combination tablet. Continue to monitor the patient closely after the fixed dose three drug combination tablet is restarted.
Drug interactions:

Nevirapine treatment should be avoided whilst rifampicin is being given for TB treatment because rifampicin reduces nevirapine levels, increasing the risk that a nevirapine-based combination will fail to control HIV.

Antifungal agents other than ketoconazole should be given to patients who require antifungal treatment while on nevirapine/d4T/3TC, since nevirapine-containing regimens may reduce blood levels of ketoconazole by more than 50%.

Patients taking clarithromycin for MAI should be monitored closely while on nevirapine/stavudine/lamivudine because there is some interaction between clarithromycin and nevirapine.

There is an increased risk of side effects if amoxicillin or erythromycin are taken with nevirapine-containing regimens.

Patients taking methadone may need to be given increased doses (up to 150 mg per day) to avoid withdrawal as nevirapine may lower methadone blood levels.

Blood levels of beta blockers, doxycycline, felodopine, griseofulvin, metronidazole, nifedipine, quinidine, steroids, theophylline, and warfarin may be decreased in patients taking nevirapine-containing regimens.

Patients on foscarnet or ganciclovir should not take 3TC-containing regimens.
Pregnancy and breastfeeding on this combination

- These drugs unlikely to harm unborn child – but evidence is limited
- The use of triple therapy substantially reduces the risk of mother to child transmission during pregnancy
- Treatment during the first trimester may carry higher risk of harm to unborn child
- Effectiveness of preventing transmission through breastfeeding unknown

Contraception: Nevirapine/d4T/3TC may reduce the effectiveness of oral contraceptives. Women who wish to avoid pregnancy should use additional or alternative methods of birth control.

Pregnancy: Pregnancy, or the desire to become pregnant, should not preclude the use of nevirapine/d4T/3TC in women unless the risk of adverse effects in the mother, fetus or infant outweighs the expected benefit to the woman concerned.

Nevirapine and 3TC have been used extensively in the prevention of mother to child transmission without a higher than normal incidence of adverse events. Observational studies suggest that pregnant women taking d4T-containing regimens may be at an increased risk of lactic acidosis and should be monitored more closely.

The use of nevirapine/d4T/3TC should have improved efficacy over short-course antiretroviral treatment in preventing mother-to-child transmission of HIV. Nonetheless, a pregnant woman should be advised that the relative risk/benefits of the combination regimen to herself and her foetus is unknown. Women not yet on therapy may wish to postpone starting treatment until the second trimester.

Lactation: WHO recommends that women who require antiretroviral treatment and who are breastfeeding should continue their antiretroviral treatment regimen. It is unknown whether stavudine is excreted in human breast milk however animal studies suggest that it might be. Nevirapine and lamivudine are present in breast milk. Nevertheless, it is unclear whether the levels of any of these drugs in breast milk are adequate to have a protective or harmful effect on the infant.

Paediatrics: The doses designed for adults are not suitable for children under the age of 14. The doses needed to be adjusted according to body weight.
1. What are the names of the drugs and what are the doses according to weight?
   ■ Answer
2. How are the drugs dosed during the first 14 days?
   ■ Answer
3. What are the most serious side effects and how should these be dealt with?
   ■ Answer
4. What are the important drug interactions?
   ■ Answer
5. What is the effect of nevirapine on the contraceptive pill?
   ■ Answer
6. Is this combination safe for pregnant women?
   ■ Answer

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