



## **Nevirapine, zidovudine and lamivudine**

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**Information on starting treatment with**

**nevirapine**  
+  
**zidovudine**  
+  
**lamivudine**

Three drugs combined in fixed dose tablets

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## Information on starting with

Nevirapine/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. Nevirapine is a non-nucleoside reverse transcriptase inhibitor.

### Fixed dose combinations of these drugs include:

- Duovir-N (Cipla) contains all three drugs
- Zidovex-LN (Aurobindo/Imunus) contains all three drugs
- Combivir (Glaxo Smith Kline) contains zidovudine (AZT) and lamivudine (3TC)
- Duovir 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)

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### Lead in dosing for the first 14 days <sup>(1)</sup>

- Nevirapine must be given separately 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 used at full dose
- Nevirapine dose must not increase until serious rash declines

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## Lead dosing for the first 14 days

### Dosage:

- Nevirapine: 200mg once a day (for the first two weeks\*); afterwards 200 mg twice a day
- Zidovudine (AZT): 300mg twice daily. Patients with impaired kidney function or who require dosage adjustment due to toxicity cannot use the fixed dose tablets.
- Lamivudine (3TC): 150mg twice daily.

\*Nevirapine should be introduced at half dose for 14 days to reduce the risk of serious rash. Note that during this period, the fixed dose tablet *must not* be used. Do not try to use one fixed dose tablet per day because it could lead to resistance to lamivudine and treatment failure. Instead, start with the separate tablets. After 14 days, the nevirapine dose should be increased to 200mg twice daily, or the fixed dose tablet can be used.

Fixed dose zidovudine/lamivudine tablets are not suitable for those with renal insufficiency or for those who require lower zidovudine doses due to adverse events.

### Baseline tests

If possible, conduct liver function tests prior to starting lead-in nevirapine/AZT/3TC therapy and at appropriate intervals during therapy. Do not use nevirapine in patients with greater than moderate ALT or AST abnormalities.

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**Lead in dosing for the first 14 days (2)**

Nevirapine 200mg  
once daily

+

Zidovudine/lamivudine  
combination tablet twice daily, 12 hours apart

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## Lead dosing for the first 14 days

### Administration

#### First two weeks\*:

- Twice daily\*\*: One zidovudine/lamivudine combination tablet  
plus
- Once daily: One tablet of nevirapine (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 a fixed dose tablet containing nevirapine (Duovir-N or Zidovex-LN) until the rash has resolved.

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### Dosing schedule after day 14

Switch to fixed dose tablet combining all three drugs if available

OR

Nevirapine 200mg  
(one tablet) twice daily  
+  
ZDV/3TC  
combination tablet twice daily

Take all medication twice daily, 12 hours apart

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## Dosing schedule after day 14

After two weeks (or rash has resolved)

- **Twice daily\*\***: One Duovir-N or Zidovex-LN tablet

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

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### 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.
- Hypersensitivity reaction: rash preceded by fever, joint pain and swelling, hepatitis. Stop all treatment immediately. When treatment resumes, use efavirenz instead of nevirapine.
- Severe liver enzyme elevations: symptoms – jaundice, pain in liver & abdomen, nausea, vomiting
- Stop treatment until normalised or change to another drug (efavirenz or abacavir) or refer to district hospital for treatment change
- At higher risk: female, older age, high alcohol use, hepatitis B or C coinfection

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## Nevirapine side effects and monitoring

**Side effects:** The combination of nevirapine/AZT/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 mucosa, and is accompanied by fever and chills. If skin peeling occurs, hospital admission and fluid replacement treatment is recommended.

**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.

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### Other side effects <sup>(1)</sup>

#### Occasional but life threatening

- **Pancreatitis**
  - Sharp pain below stomach, nausea, vomiting, fever
  - Very rare with these drugs – linked to 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**
  - If neutrophil count < 500/ml, consider switch from ZDV

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## Other side effects

**Pancreatitis:** Lamivudine has been associated rarely 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 generalized fatigue and weakness. These may be 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/district level if these symptoms develop.

**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.

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### Other side effects <sup>(2)</sup>

#### Possible long-term

- Fat loss from limbs and face (lipoatrophy)  
(best to switch from zidovudine to tenofovir or abacavir)

#### Anaemia

- Caused by ZDV
- High risk in patients with anaemia before treatment, women may be at higher risk
- Monitor haemoglobin, or for paleness, tiredness
- Severe anaemia – blood transfusion, switch from ZDV if possible
- Moderate anaemia – reduce ZDV dose, discontinue fixed dose combination tablet and use separate formulations for each drug until anaemia improves
- Long-term reduced ZDV dose not recommended, will lead to treatment failure, resistance

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## Other side effects

**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. 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 treatment discontinuation.

**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.

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**Other side effects** (3)

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

- **Headache**
  - Common in first weeks of 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

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## 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), 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).

**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.

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 AZT/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 higher dose or fixed combination tablet. Continue to monitor the patient closely after the higher dose is restarted.

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**Drug interactions** (4)

- Avoid nevirapine whilst receiving rifampicin for TB treatment
- Use antifungals other than ketoconazole
- Clarithromycin and nevirapine: monitor liver enzymes; CL may increase NVP 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

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## Drug interactions

**Drug interactions:** Nevirapine-based treatment should be delayed until rifampicin treatment for TB is completed, since rifampicin may reduce nevirapine levels, leading to failure of HIV treatment.

Antifungal agents other than ketoconazole should be given to patients who require antifungal treatment while on nevirapine/AZT/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/AZT/3TC 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. At the same time, methadone may increase blood levels of zidovudine two-fold. Patients experiencing zidovudine-related adverse events may need dose reductions.

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

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### Drug interactions (2)

- Cotrimoxazole may increase risk of neutropenia and anaemia when taken with ZDV
- Anti-convulsants: ZDV reduces phenytoin levels, valproic acid increases ZDV levels
- Nevirapine may reduce oral contraceptive levels

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## Drug interactions

Alpha-interferon, ganciclovir, cancer chemotherapeutics co-trimoxazole and other drugs that have bone marrow effects may increase the likelihood of zidovudine's haematologic toxicities in some patients with advanced HIV disease. Haematologic 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.

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### Pregnancy and breastfeeding

- AZT/3TC/NVP is likely to substantially reduce risk of MTCT transmission compared to AZT or NVP alone if taken:
  - During pregnancy
  - During breastfeeding

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## Pregnancy and breastfeeding

**Contraception:** Nevirapine/AZT/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/AZT/3TC in women unless the risk of adverse effects in the mother, foetus or infant outweighs the expected benefit to the woman concerned.

There have been no large studies of the combination of nevirapine/AZT/3TC in pregnant women and there are insufficient data to definitively determine the associated risk of birth defects in humans during the first 10 to 12 weeks of gestation. However, animals provide some data for the safety of the individual drugs in pregnancy; and pharmacokinetic studies indicate that no dose modifications are required for pregnant women.

Furthermore, all three drugs have been used extensively in the prevention of mother to child transmission without a higher than normal incidence of adverse events.

The use of nevirapine/AZT/3TC should have improved efficacy over short-course antiretroviral treatment in preventing mother-to-child transmission of HIV if it is taken throughout the second and third trimesters and post-partum. 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 at least the second trimester.

**Lactation:** WHO recommends that women who require antiretroviral treatment and who are breastfeeding should continue their antiretroviral regimens. All three drugs are present in breast milk. Nevertheless, it is unclear whether the levels of any of these drugs in breast milk are present in sufficient amounts to have either a protective or a harmful effect on the infant.

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### Test questions

1. What are the names of the drugs?
2. How are the drugs dosed during the first 14 days?
3. What are the most serious side effects and how should these be dealt with?
4. What are the important drug interactions?
5. What is the effect of nevirapine on the contraceptive pill?
6. Is this combination safe for pregnant women?

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## Test questions

1. What are the names of the drugs?
  - 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](http://www.aidsmap.com)