

Getting spine: the nucleoside backbone

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[Nucleoside analogues](#) [1]A type of anti-HIV drug that works by inhibiting a stage of the HIV life cycle called reverse transcription. Non-nucleosides work in a similar way, but are chemically different. are the backbone of successful anti-HIV treatments. This article examines some of the issues involved in selecting the best nucleoside backbone.

The success of modern anti- HIV treatment depends on taking a multi-pronged approach to stopping HIV replication.

Most people on treatments take a cocktail of three or four antiretroviral drugs, of which two will be from the nucleoside analogue group. This issue's Backgrounder looks at the nucleoside analogues, and explains some of the criteria you and your doctor need to consider when choosing a nucleoside backbone.

Nucleoside analogue reverse transcriptase inhibitors – to give them their full, tongue-twisting, name – are a group of drugs which inhibit (block the action of) an enzyme called reverse transcriptase which HIV uses to replicate inside our cells. Because they are structurally similar to nucleosides (one of the building blocks of DNA) they are called nucleoside analogues.

Because their full name doesn't exactly trip off the tongue, you'll often hear this group of drugs referred to as 'nucleosides', 'NRTIs' or 'nukes'. Although it's not technically a nucleoside, for this article we'll also include tenofovir (Viread), a nucleotide analogue reverse transcriptase inhibitor.

There are currently seven drugs approved in Australia in the nucleoside group – AZT (zidovudine/Retrovir), ddI (didanosine/Videx EC), d4T (stavudine/Zerit), 3TC (lamivudine), abacavir (Ziagen), FTC (emtricitabine/ Emtriva) and tenofovir. (An eighth nucleoside analogue, ddC (zalcitabine/Hivid), is currently being phased out and will no longer be available after the end of 2006).

While the nucleosides are not generally as potent as other antiretroviral drugs they are of tremendous importance in HIV treatment. Standard treatment always includes some drugs from this class – usually two nucleosides plus either a non-nuke or a protease inhibitor – which means virtually all people on treatment in Australia will be taking at least a couple of the drugs listed above.

Because nucleoside analogues are the common thread which runs through all standard [HAART](#) [2]Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together. combinations, they are referred to as the nucleoside backbone – the foundation on which the combination is built. There are a number of issues you and your doctor need to consider when selecting a nucleoside backbone.

The ability of the drugs to suppress HIV replication – their **efficacy** – is the first thing to consider. All drugs approved for use in Australia have been shown in clinical trials to be effective in this regard, however none is able to completely suppress HIV on its own.

Because of similarities in the way they work, AZT and d4T are not usually recommended to be used together; the same goes for 3TC and FTC. [Clinical](#) [3]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. trials have also shown poor CD4 count improvements when tenofovir and ddI are used in combination, so this pairing is also no longer recommended.

Because not all HIV drugs are able to cross the [blood-brain barrier](#) [4]A selective barrier (obstacle) between circulating blood and brain tissues that prevents damaging substances from reaching the brain. Certain compounds readily cross the blood-brain barrier; others are completely blocked., **central nervous system (CNS) penetration** is another consideration. Having at least one drug in the combination which can get into the brain and spinal fluid is strongly recommended to suppress HIV replication in these parts of the body.

AZT and abacavir are both known to penetrate into the CNS, and AZT has been shown to substantially reduce the risk of developing HIV-associated brain diseases such as dementia. To a lesser extent, d4T, 3TC and ddI have also been shown to cross into the CNS, although their [effectiveness](#) [5](Of a drug or treatment). The maximum

ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the standard procedure, Phase II clinical trials gauge efficacy, and Phase III trials confirm it. In preventing HIV-associated brain disease remains unproven.

As with all drugs, it's important to consider **resistance** when choosing a nucleoside backbone, and some nucleosides are cross-[resistant](#) [6] HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. with other drugs in the class. Unlike the other [drug classes](#) [7] A group of anti-HIV drugs with the same target of action. Anti-HIV drug classes include *nucleoside analogue reverse transcriptase inhibitors*, *protease inhibitors* and *non-nucleoside analogue reverse transcriptase inhibitors*, as well as several others. Combining drugs from three or more classes is the basis of Highly Active Antiretroviral Therapy (HAART)., however, resistance to nucleosides is sometimes a two-way street.

For example, the main form of 3TC resistance (the M184V mutation) can also result in resistance to ddC, abacavir and ddl, but can also result in increased susceptibility (the opposite of resistance) to AZT, d4T and tenofovir.

Similarly, the K65R mutation, which occurs in people who have taken tenofovir, abacavir or ddl, leads to resistance to tenofovir and ddl but increased susceptibility to AZT and the non-nucleosides.

Because resistance is rarely 100 percent, and because it is difficult to measure, choosing the best [antiretrovirals](#) [8]

Another consideration is **dosing requirements**. All the drugs in this class are taken once or twice a day and only ddl has special dietary requirements (it should be taken on an empty stomach).

Once-daily options are abacavir, 3TC, FTC, and tenofovir.

Several multi-drug combinations are available which combine several nucleosides into the same pill, reducing the number of pills you have to take. Combivir (AZT plus 3TC, one tablet twice a day), Kivexa (abacavir plus 3TC, one tablet once a day) and Trizivir (AZT, 3TC and abacavir, one tablet twice a day) are all available now, and Truvada (tenofovir plus FTC, one tablet once a day) is in the approval pipeline.

A final consideration is **side effects**. Different drugs in this group tend to cause different side effects and may be better tolerated by some people than others.

The drugs which have the lowest levels of reported side effects are 3TC, tenofovir and FTC. At the other end of the scale, d4T has fallen from popularity because of its side effects, notably lipoatrophy (loss of fat from the face, arms and legs).

Nausea, vomiting and gastrointestinal disturbances are the most common side effects among drugs in this group, especially during the initial period after starting treatment. AZT, ddl and abacavir seem to be the main offenders. These side effects can often be reduced by taking anti-nausea medications or using [complementary therapies](#) [9] A broad range of healing philosophies, approaches, and therapies that Western (conventional) medicine does not commonly use to promote well-being or treat health conditions. Examples include acupuncture, herbs, Traditional Chinese Medicine, etc..

Peripheral neuropathy is a painful condition in which the feet and hands burn and tingle. It starts gradually, sometimes as a 'pins-and-needles' sensation, and can become extremely painful. Peripheral neuropathy has been most commonly reported in people who take the 'd' drugs – ddl, d4T and ddC – and if it occurs usually requires a change of drugs. The risk of developing this side effect is greatest when ddl and d4T are taken together.

Less common, but more serious side effects associated with nucleoside drugs include pancreatitis (usually with ddl), abacavir hypersensitivity reaction (abacavir), lactic acidosis (any nucleosides) and kidney toxicity (tenofovir). Fortunately, these life-threatening side effects are very rare, however you should always be aware of them when starting treatment and see your doctor immediately if you are concerned by any side effect.

Nucleoside form guide

Here's a brief guide to some of the most popular nucleoside combinations. Not every combination is listed and there may be additional reasons why some combinations are or are not right for some people – your doctor will

recommend the most appropriate combination for your circumstances and should be happy to explain the reasons behind the choice.

AZT plus 3TC: one of the most widely-prescribed combinations. Available (as Combivir) in a single tablet. Twice daily. One of the most widely-studied combinations with numerous clinical trials demonstrating efficacy. Possible side effects include nausea, [anaemia](#) [10] A lower than normal number of red blood cells. and lipodystrophy.

Abacavir plus 3TC: similar or slightly better efficacy compared to AZT plus 3TC. Now available (as Kivexa) in a single tablet. Once daily. Generally well tolerated, but about 5 percent of people will develop a hypersensitivity reaction to abacavir which will rule this combination out for them.

FTC plus tenofovir: a relative newcomer to the field, this combination is the rising star. One tablet and one capsule taken once daily (a combination pill, Truvada, is available overseas and should be available in Australia soon). One of the best choices in terms of side effects – in a clinical trial comparing this combination with AZT/3TC, FTC/tenofovir came out ahead because of its better tolerability.

3TC plus tenofovir: similar efficacy to FTC/tenofovir, also with relatively few side effect issues. A good option for people coinfecting with hepatitis B.

d4T plus 3TC: a former favourite, better tolerated and similar efficacy to AZT/3TC, but concerns about lipodystrophy from the d4T mean this combination has fallen from favour.

ddl plus 3TC/FTC: clinical trials have shown that these combinations are effective, but they are not usually recommended. Food restrictions and possible long-term side effects have reduced ddl's popularity in favour of newer, more convenient drugs, plus ddl's strength is that it can be used after 3TC/FTC resistance occurs.

- [abacavir](#)
- [Combivir](#)
- [didanosine \(ddl\)](#)
- [drug resistance](#)
- [emtricitabine \(FTC\)](#)
- [Kivexa](#)
- [lamivudine \(3TC\)](#)
- [NRTIs](#)
- [starting treatments](#)
- [stavudine \(d4T\)](#)
- [Trizivir](#)
- [zalcitabine \(ddC\)](#)
- [zidovudine \(AZT\)](#)

Links:

[1] <http://www.napwa.org.au/glossary/term/104>

[2] <http://www.napwa.org.au/glossary/term/96>

[3] <http://www.napwa.org.au/glossary/term/475>

[4] <http://www.napwa.org.au/glossary/term/415>

[5] <http://www.napwa.org.au/glossary/term/486>

[6] <http://www.napwa.org.au/glossary/term/109>

[7] <http://www.napwa.org.au/glossary/term/124>

[8] <http://www.napwa.org.au/glossary/term/122>

[9] <http://www.napwa.org.au/glossary/term/478>

[10] <http://www.napwa.org.au/glossary/term/402>