



The Information Exchange

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COMBINATION THERAPY: How do anti-HIV drugs work?

At present there are no anti-HIV drugs available that can eradicate or kill the virus throughout the body. The drugs that are available reduce the speed at which HIV reproduces itself. The goal of antiretroviral therapy in HIV infection is to reduce the amount of replicating virus to as low a level as possible, for as long as possible, in all sites where HIV infected cells are present. This will help prevent infection of new cells and further damage to the immune system.

The amount of replicating virus in the blood can be measured using a simple blood test, called a viral load test. In practical terms the aim of antiretroviral therapy is to reduce the viral load to below the level of detection of the test; the most commonly used test can detect virus particles down to 50 copies of the virus per ml. If your viral load is lower than this, the result is referred to as 'undetectable'.

There are now 7 classes of antiretroviral drugs available in the UK, from which to select a combination. Drugs have a trade name (signified by ®) as well as a chemical name. Generally in the UK doctors talk about the chemical name of the drug, but in the case of the pills which have more than one chemical, the trade name is usually used. Your doctor will select a medication regimen for you by combining drugs from some of the following classes. Combination regimes are commonly referred to as highly active antiretroviral therapies or HAART for short.

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Nucleoside analogues or nucleoside reverse transcriptase inhibitors (NRTIs) are sometimes referred to as the 'backbone' of a combination, and nearly all patients starting therapy will have at least 2 drugs from this class in their regime. HIV is unable to reproduce by itself - it needs a human cell to manufacture new viral particles. The virus enters a healthy CD4 cell. Once inside the cell the virus converts its own material into DNA using the enzyme reverse transcriptase. This new DNA then acts as a blueprint, directing the infected cell to make new virus particles. The new virus particles are then released and can infect other healthy cells. Inside the cell, NRTIs are converted into their active form – the triphosphate form by a process called phosphorylation. In their active form they can block the action of the reverse transcriptase enzyme. NRTIs currently available are:

- Abacavir (Ziagen®)
- Didanosine, or ddI (Videx®)
- Emtricitabine or FTC (Emtriva®)
- Lamivudine or 3TC (EpiVir®)
- Stavudine or d4T (Zerit®)
- Zidovudine or AZT (Retrovir®)
- Combivir® is a combination of both lamivudine and zidovudine in one tablet
- Trizivir® is a combination of lamivudine, zidovudine and abacavir in one tablet
- Kivexa® – a combination of abacavir and lamivudine
- Truvada® – a combination of emtricitabine and tenofovir
- Atripla® is a combination of emtricitabine and tenofovir and an NNRTI efavirenz.

2. Nucleotide Reverse transcriptase inhibitors (NtRTIs)

This class of drug works in exactly the same way as NRTIs, with the exception that an extra phosphate is attached to the drug molecule. This means that the drug is present in a more active form, as it does not have to be phosphorylated in the same way as NRTIs do. It also may be active in more types of cells within the body. At present the only antiretroviral drug available in this class is

- Tenofovir (Viread®)

3. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs also block the action of the reverse transcriptase enzyme – but by binding onto a different site from the NRTI or NtRTI drugs. NNRTIs currently available are:

- Efavirenz (Sustiva[®])
- Nevirapine (Viramune[®])
- Etravirine (Intelence[®])

4. Protease Inhibitors (PIs)

Protease is another of HIV's enzymes; its role is to break up the long chains of HIV proteins that are produced inside infected cells. Protease inhibitors prevent protease from cutting the protein chains into the shorter pieces that HIV needs to make new virus particles. By working in this way protease inhibitors reduce the number of new active copies of HIV that can infect other cells. Most PIs need to be given with ritonavir to ensure sufficient levels of medication in the body. PIs currently available are:

- Atazanavir (Reyataz[®])
- Darunavir (Prezista[®])
- Indinavir (Crixivan[®])
- Fosamprenavir (Telzir[®])
- Nelfinavir (Viracept[®])
- Lopinavir and ritonavir (Kaletra[®])
- Ritonavir (Norvir[®])
- Saquinavir (hard gel capsules or tablets: Invirase[®])
- Tipranavir (Aptivus[®])

5. Fusion Inhibitors

Fusion inhibitors are an entirely new class of drug. They block the process by which HIV enters the cell. Because they block HIV in a completely different way to any of the other drugs currently available, there is thought to be no cross resistance to other drugs. At present enfuvirtide (Fuzeon[®]), also known as T20 is the only available drug in this class. T20 is manufactured as an injection only at present.

6. CCR5 Antagonist

CCR5 inhibitors work by blocking a receptor on the surface of cells. This prevents the cell from being infected with HIV. Some people who have received a lot of anti-HIV treatment in the past aren't suitable for treatment with CCR5 inhibitors. A test can tell if CCR5 treatment will work for you.

- Maraviroc (Celsentri[®])

7. Integrase Inhibitors

Integrase inhibitors block the action of integrase, an enzyme that integrates genetic material from the virus into its target cell.

- Raltegravir (**Isentress[®]**)

This information was prepared by the HIV/GUM pharmacy department at the Chelsea and Westminster Hospital. If you have any queries regarding the information, please call Kobler Pharmacist on 020 3315 5604

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