

resistance

After a person is infected with HIV, many different strains of the virus appear over time as the virus copies itself (replicates). Each new generation has tiny differences, or mutations, in its structure. Some of these mutations occur in the parts of HIV which are targeted by anti-HIV drugs. This can result in strains of HIV that are less sensitive to treatment.

When an anti-HIV drug is started, the viruses that are highly sensitive to the drug disappear rapidly. This leaves behind strains that can copy themselves despite the drug's presence. In time, the 'pool' of viruses will include fewer and fewer drug-sensitive strains and more and more resistant ones. These may or may not be capable of harming the body.

It is also important to note that as many as 25% of all people newly infected with HIV in the UK have been infected with a strain of HIV resistant to at least one anti-HIV drug, and that resistant virus can remain the dominant form of HIV years after infection, possibly limiting treatment options.

Minimising the risk of resistance

It's important to take anti-HIV drugs exactly as prescribed, by sticking rigidly to the recommended dose and timetable, and observing instructions about food. Taking too little drug (by missing or reducing doses) could allow drug levels in the blood to fall to inadequate levels, allowing viral replication to occur and increasing the risk of the emergence of resistance.

Using three or more anti-HIV drugs at once, known as combination therapy or 'HAART', delays resistance, because viruses that are resistant to one of the drugs may still be controlled by the others.

Studies have shown that the risk of viral load rebound is related to the lowest point to which viral load falls after starting treatment, called the 'nadir'. The lower the nadir, the lower the risk of rebound, and therefore the risk of resistance. People whose viral load falls to, and remains below 50 copies are at a much lower risk of developing resistance. However, resistance may emerge even in these people over the longer term.

Adding or changing a single new drug in a combination which is not suppressing viral load is likely to lead to the development of drug resistance, because the impact of that single new drug is likely to be insufficient to block replication. Experts now advise that treatment changes in

these circumstances should involve switching to a completely new combination, wherever possible.

Continuing with the same drugs after your viral load begins to go up can also encourage the development of resistance. This is because resistance to some drugs develops progressively; as more resistance mutations accumulate, sensitivity to the drug will fall. However, resistance to drugs emerges at different speeds. For example, 3TC, nevirapine and efavirenz resistance emerges very quickly, but d4T and ddC resistance emerges more slowly.

Also, people whose viral load remains high or rebounds whilst taking anti-HIV drugs may still experience a sustained rise in CD4 count, and delayed disease progression, though the reason why this occurs is not well understood. Whilst resistance is one reason for viral load rebound, it is not the only reason.

Cross-resistance

Single mutations or sets of mutations in the virus can produce resistance to several different drugs within the same class. This means that once resistance to one drug has emerged, this virus population may also be resistant to drugs you haven't taken yet. This is called cross-resistance and affects all anti-HIV drug classes. For example, it is possible that if you develop resistance to a non-nucleoside reverse transcriptase inhibitor (NNRTI), you will also be resistant to all others in the same group. Again, remaining on a regimen which is failing to suppress viral load to undetectable levels may well lead to cross-resistance.

Resistance testing

Tests have been developed which aim to detect which anti-HIV drugs you are resistant to, and your level of resistance to them. It is now recommended that a resistance test is used whenever an HIV drug combination is changed in order to guide selection of the new combination. The results should be considered as part of a full patient history, which takes account of the range of possible causes for the previous combination's failure. Doctors are currently working out the best way to use resistance tests, and interpreting them is not always straightforward and should be undertaken by an expert. See NAM Factsheet 46, Resistance Tests.

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