

Breaking the drought

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It's been a while since there was much cause for excitement in the drug pipeline, and even now there's just one anti-HIV drug nearing the end of the development maze. But, says KIRSTY MACHON, a new generation of HIV treatments promises to break the drought.

A few years ago, the HIV drug development landscape seemed rather barren, littered with unimpressive 'me-too' drugs, second-generation drugs from already-existing classes, noble and ignoble failures, and even one or two obscure compounds withdrawn for depressing-sounding reasons such as "unacceptable kidney toxicity in dogs."

With the notable exception of T-20 (enfuvirtide) – which did not exactly enjoy a seamless journey through the drug development phase – there were few drugs which appeared to offer a genuinely innovative or new approach to HIV treatment.

In the last two years, however, things seem to have changed: several important and promising new treatment options have appeared on the radar. This article will focus on three areas of development that seem especially encouraging, each at a different stage of development: tipranavir, a group of drugs called DAPYs, and the CCR5 attachment inhibitors.

Protease: the next generation

Manufactured by Boehringer Ingelheim (who also make the non-nuke nevirapine), tipranavir is a new [experimental](#) [1](Of a drug) Not licensed for use in humans, or as a treatment for a particular condition. Experimental drugs are studied in clinical trials to determine their safety and efficacy, and are sometimes made available via Special Access Schemes prior to their approval. protease inhibitor (PI) which is in an advanced stage of development. It has already been extensively researched throughout the world, and several [phase 3](#) [2]A large clinical trial designed to establish whether a drug is effective and safe enough for widespread use. Phase III studies include expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling. [clinical](#) [3]Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. studies have delivered interim reports.

Of all the drugs in this article, tipranavir is probably the closest to the end of the development process, with marketing applications already lodged in the United States and Europe, and an Australian licensing application expected to follow in due course.

Originally developed by Pharmacia and Upjohn, tipranavir's development has been marked by several setbacks to the research process, and the compound was eventually sold to Boehringer.

It is currently available in Australia through an 'emergency access' program, and is also being provided to Australian patients who were involved in clinical studies. The emergency access program is currently very limited – much more so than has been the case with many previous drugs: only people with fewer than 100 T-cells and viral loads over 10,000 qualify for this program. Tipranavir has been available under much less restrictive criteria to UK patients since last June, and in the US since December, and there are ongoing negotiations with the company to widen access here.

Like other PIs, tipranavir has been investigated as part of combination treatment for HIV. Unlike other PIs however, tipranavir has a novel 'non-peptidic' molecular structure which is designed to make it effective against [virus](#) [4]A small infective organism which is incapable of reproducing outside a host cell. which has become [resistant](#) [5]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. to existing drugs in this class. The developers of this drug also hope that non-peptidic PIs will be less likely to lead to resistant virus themselves.

Because of this, the main focus of research on tipranavir (and the likely first widespread use of the drug once it becomes available) is in [salvage](#) [6][salvage therapy] A treatment strategy for managing HIV in people who have developed resistance to existing therapies. therapy, for people who are resistant to existing treatments and in need of new treatment options.

As with other PIs, people taking tipranavir often report gastrointestinal disturbances as the most common [side effect](#) [7]An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time. (around 45 percent of people develop diarrhoea). Tiredness, nausea, headache and vomiting can also occur.

People taking tipranavir in clinical trials have been observed to have increased liver enzymes ([ALT](#) [8]alanine transaminase or alanine aminotransferase, an enzyme involved in the metabolism of the amino acid alanine. Elevated ALT levels in the blood may indicate liver injury or disease such as hepatitis. Also called SGPT (serum glutamate pyruvate transaminase), AST, etc) but these were usually mild and did not cause any illness or lead to people stopping the drug. Like most other PIs, tipranavir also leads to increased [blood fat](#) [9]A fat. ([triglyceride](#) [10]

Designer molecules: finessing old targets

One of the major concerns about so-called 'me-too' drugs (which target the same parts of the HIV life cycle as existing [antivirals](#) [12]A medication or substance which is active against one or more viruses. May include anti-HIV drugs, but these are more accurately termed antiretrovirals.) is the phenomenon of cross-resistance or multiple drug resistance. Mutations to HIV which occur over time can make the virus partly or wholly resistant to not just one particular drug but several or all of the drugs in a class.

For example, resistance to any one of the current non-nucleoside drugs typically means resistance to the other two drugs in this class. So if you're resistant to nevirapine, you'll probably be resistant to efavirenz as well – which can seriously limit your treatment options for the future.

The problem with HIV is that it's a 'moving target': rapid evolutionary or genetic change creates opportunities for treatment resistance to develop. Researchers are now turning to cutting-edge chemistry to see whether it's possible to engineer drugs in such a way that it's more difficult for HIV to develop resistance to them.

There are two broad approaches which might work here: you could design drugs to more effectively inhibit mutant HIV, or you could design drugs which target the 'conserved' areas of the HIV genome—those which tend to undergo the least genetic instability and variation.

The Belgian drug company Tibotec (part of the global pharmaceutical manufacturer Johnson and Johnson) is pursuing the first approach, setting out in ardent pursuit of new chemical compounds which might be effective against resistant virus.

These drugs target the same parts of the HIV life cycle as existing drugs, but they are designed to incorporate a degree of 'molecular flexibility' that would enable them to accommodate small genetic changes in the target areas of the HIV genome, making it harder for HIV to become resistant to them.

The first of these drugs to undergo clinical trials was a protease inhibitor called TMC114, which has gone through several [phase 2](#) [13]A smaller clinical trial designed to establish whether a drug is effective. Phase II studies are conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks. If there is evidence that the drug is effective, a Phase III study is undertaken, with a larger number of participants, to confirm this. studies (including in Australia) and is expected to start phase 3 studies soon. Early data suggests that TMC 114 remains effective in people who have high-level resistance to other protease inhibitors.

Tibotec is also involved in the development of TMC125, a non-nucleoside reverse transcriptase inhibitor (NNRTI). An NNRTI which remains active against virus which is resistant to other NNRTIs would be a particularly valuable addition to HIV treatment. This is because of the very real problem of class resistance in the NNRTI group. The two main drugs in this class, nevirapine and efavirenz, are both highly important because they are often more tolerable than protease inhibitors, and they have good activity against HIV.

Johnson and Johnson and Tibotec are also looking at a new group of NNRTIs called DAPYs. DAPYs, short for

diarylpyrimidines have been developed at New York's Rutgers University using cutting-edge molecular modelling techniques to target HIV in such a way that they could overcome some of the problems faced by older HIV drugs (like poor [bioavailability](#) [14]The extent to which an oral medication is absorbed in the digestive tract and reaches the bloodstream, thereby permitting access to the site of action. and long half-lives, and limitations in the formulations which make it easier for HIV to mutate around).

These still-experimental drugs are still at the very earliest stages of development, but the early results of test-tube studies have been staggering, with single drugs suppressing HIV as effectively as existing three and five drug combinations, and with inbuilt molecular flexibility that enables them to adjust to changes in the virus's molecular structure. Professor Eddy Arnold, one of the leaders of the Rutgers team, described the DAPYs as "rolling with the punches, wiggling and jiggling around" to fit the unique molecular makeup of each HIV particle.

DAPYs are a long way from becoming part of routine therapy (just getting them this far has taken over ten years) but they give a glimpse of the changing ways in which drugs are developed. As a recent article in the Journal of Medicinal Chemistry enthused: "The discovery ... was the result of a coordinated multidisciplinary effort involving medicinal chemists, virologists, crystallographers, molecular modellers, toxicologists, analytical chemists, pharmacists, and many others".

Attachment inhibitors: finding new targets

Before HIV can enter and infect individual cells, it must first attach itself to the cell surface. It does this in several steps, first by binding to a chemical marker called CD4, then to one of two chemokine receptors, called CCR5 and CXCR4. Once HIV has locked on to two points, it is able to break into the cell.

Drugs that interfere with this process by locking onto the CCR5 or CXCR4 'co-receptors' before HIV gets to the cell are called 'attachment inhibitors'. Two drugs in this class, both of which work on the CCR5 co-receptor, are about to enter clinical trials.

A phase 2 study of Pfizer's CCR5 inhibitor, codenamed UK-427,857, is [enrolling](#) [15]The act of signing up participants into a study. Generally this process involves evaluating a participant with respect to the eligibility criteria of the study and going through the informed consent process. now in Australia. A second CCR5 inhibitor, being developed by GlaxoSmithKline, is likely to follow into trials soon.

These drugs do raise some important questions. In particular, there are some concerns that these drugs do not prevent HIV from attaching to the alternative CXCR4 chemokine receptor. While most HIV strains prefer the CCR5 route, virus which uses CXCR4 – usually only seen in the later stages of HIV disease – is believed by some researchers to be more virulent.

One virus, many targets

Perhaps the most encouraging aspect of the HIV drug development pipeline at the moment is the proliferation of drugs designed specifically to combat the problem of resistant virus, such as tipranavir, drugs with novel molecular structures, such as the DAPYs, and drugs targeting whole new stages of the HIV cycle, such as the attachment inhibitors.

If the promise of these new compounds is borne out by clinical trials (and, let's be honest, history tells us that many more HIV drugs are abandoned than ever make it to market), it's just possible that the face of HIV treatment will undergo a change as radical as that of the 'Protease Moment', with a new capacity to target HIV not just with me-too drugs offering incremental benefits and the risk of cross-class resistance, but at the many points of its complex and complicated life cycle.

- [HIV treatments](#)
- [tipranavir](#)
- [experimental treatments](#)

Links:

- [1] <http://www.napwa.org.au/glossary/term/491>
- [2] <http://www.napwa.org.au/glossary/term/92>
- [3] <http://www.napwa.org.au/glossary/term/475>
- [4] <http://www.napwa.org.au/glossary/term/125>
- [5] <http://www.napwa.org.au/glossary/term/109>
- [6] <http://www.napwa.org.au/glossary/term/111>
- [7] <http://www.napwa.org.au/glossary/term/469>
- [8] <http://www.napwa.org.au/glossary/term/80>
- [9] <http://www.napwa.org.au/glossary/term/100>
- [10] <http://www.napwa.org.au/glossary/term/114>
- [11] <http://www.napwa.org.au/glossary/term/88>
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