

Looking forward, looking back

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In September 2006, the International Association of Physicians in AIDS Care will mark a decade of highly active [antiretroviral](#) [1]A medication or other substance which is active against retroviruses such as HIV. therapy. Has it really been 10 years since the so-called Protease Moment? KIRSTY MACHON reports on where we have come from – and where to from here.

Everything changed in 1996. Dr David Ho, the brilliant doctor who would go on to be named Time magazine's 'Man of the Year', captured the world's attention with tales of a stunningly successful new approach to treating HIV infection.

Known as 'cocktail therapy', 'triple combination therapy' and eventually 'highly active antiretroviral therapy' (HAART), the new approach revolutionised HIV medicine and triggered a sudden decline in the deadly toll of AIDS, at least in those countries where the drugs were available to those who needed them.

Ho and other researchers had discovered that by treating HIV with multiple drugs from different classes, viral loads could be brought down to very low levels. With its twin slogans 'It's the [virus](#) [2]A small infective organism which is incapable of reproducing outside a host cell. stupid' and 'Hit hard, hit early', the arrival of HAART shifted HIV from a death sentence to an illness which could be 'lived with'.

Perhaps, it was whispered at the time, HIV could even be eradicated altogether by the use of treatments to maximally suppress viral replication.

But that initial burst of optimism was soon tempered with realism. Ho's first estimate – that viral eradication would take several years – was extended to several decades, then he stopped talking about it altogether. These days, no one really believes that any combination of the 22 licensed HIV drugs, or any of those in development, is capable of eradicating HIV altogether, because of HIV's ability to hide in cells where viral load can't be detected.

But there was another reason for the reality check. Those initial HAART combinations were based around drugs which presented formidable challenges to those taking them – severe side effects, huge pill burdens and complicated dosing schedules. More ominous still were the long-term toxicities such as lipodystrophy and lipoatrophy which soon started to emerge. Finally, there was the matter of the virus itself, which continued to find ways to evade the new drugs.

The emergence of these issues tarnished the image of HIV [antiviral](#) [3]A medication or substance which is active against one or more viruses. May include anti-HIV drugs, but these are more accurately termed antiretrovirals. therapy, leading many people with HIV to defer starting treatment, or not to treat at all. The combination of side effects, the need for rigorous adherence, and the possibility HIV might become [resistant](#) [4]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. anyway saw David Ho's 'hit hard, hit early' mantra fall quickly out of favour. Many people who had been positive for a long time, serially cycling through new drugs as they became available, were now interested in the possibility of treatment breaks or 'drug holidays'. Other people, newly diagnosed, hedged their bets on when and if to start treatment, often choosing to defer it as long as their CD4 count and health allowed.

What do we have to look forward to?

Ten years since David Ho made Time's cover, it seems that, once again, there is a renewed sense of treatments optimism. In part, this is driven by several new developments in research, with potentially groundbreaking new agents now appearing on the treatments horizon.

Some examples of these include CCR5 inhibitors (designed to prevent HIV from binding to human cells) and [integrase inhibitors](#) [5], a promising new class of drug which targets a different stage in HIV's lifecycle and which have, in [Phase II](#) [6]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, been very well tolerated with no signs of major side effects so far.

Having said that, [phase 3](#) [7] 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. Studies of Merck's integrase inhibitor are just getting underway now, and two of the three candidate CCR5 inhibitors which were being studied twelve months ago have been withdrawn from development due to toxicity problems. The one left standing, being developed by the global giant Pfizer, is now drawing towards the final stage of its research program.

A similar fate has befallen another new agent, once thought to be of great promise, a nucleoside analogue known as Reverset, which is no longer being developed due to serious limitations with and reservations about the quality and outcomes of earlier trials.

Further back down the line, there are some other new approaches being considered. [PA-457](#) [8], the first drug in a new class of "maturation inhibitors":[/?q=taxonomy/term/239'](#), is designed to interfere with HIV at the crucial last stages of its lifecycle, where new viral copies are assembled, just before they leave the infected cells to go on and infect others.

Finally, there are the much-vaunted 'next generation' drugs, advanced forms of technical and chemical wizardry in existing [drug classes](#) [9] 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).. Among these drugs is [darunavir](#) [10] (TMC-114), a protease inhibitor newly available in Australia through a [special access scheme](#) [11] Before a drug has been approved, manufacturers often provide the drug free of charge to people who cannot participate in a clinical trial and who meet certain criteria under a Special Access Scheme (SAS). , and which is held to be a promising new agent on the evidence so far. Newer and better non-nucleosides and proteases are also under development.

Working better with what we have

There is another, perhaps more important, aspect to this renewed treatments optimism. In essence, it's the fact that clinicians and researchers, after many years, are now more skilled than ever before at working with the drugs we already have.

Long-term toxicities are a case in point. It wasn't so long ago that it was thought almost inevitable that people with HIV would, at some point, face the spectre of [lipoatrophy](#) [12], the characteristic facial fat loss strongly associated with certain anti-HIV drugs (the thymidine analogues, notably d4T, ddI and D4T). For people starting treatment today, the likelihood of developing lipoatrophy is greatly reduced.

For a start, there has been a switch away from the thymidine analogues in favour of newer drugs, such as tenofovir, 3TC, FTC and abacavir, which do not appear to have an association with this often privately-debilitating physical change. Further, the capacity to screen for patients who may be at risk of developing the potentially serious hypersensitivity reaction to abacavir (which had often led people to avoid this drug) means that there are much more advanced and well-studied options now for people who are selecting their first line combinations.

Obviously, all HIV drugs carry potential risks (tenofovir, for example, has been linked to kidney problems in a small number of patients) but the availability of more tolerable combinations which do not bear the same risk of lipoatrophy is a significant step forward and one we should celebrate. Many positive people point to a fear of lipoatrophy as one of the main reasons they have been reluctant to start antiviral treatment.

Another reason for optimism is the emergence of fixed-dose combinations – two or more agents combined into one pill – which can be dosed just once a day, many of which have fewer side effects. From the early days when it was not uncommon for people to be taking more than 30 pills a day, these days for many people on their first or second combinations it's possible to effectively treat HIV with just three, or even two, pills – a fixed-dose

nucleoside combination (Combivir, Truvada or Kivexa), plus a non-nucleoside (nevirapine or efavirenz), for example.

In the United States, the [Food and Drug Administration](#) [13] The U.S. Department of Health and Human Services agency responsible for ensuring the safety and effectiveness of all drugs, biologics, vaccines, and medical devices, including those used in the diagnosis, treatment, and prevention of HIV infection, AIDS, and AIDS-related opportunistic infections. The FDA also works with the blood banking industry to safeguard the nation's blood supply. The Australian equivalent is the Therapeutic Goods Administration (TGA). is considering an application to approve a single pill combination of tenofovir, FTC and efavirenz – once approved, this will be the first single-pill, once-a-day HAART regimen.

These simpler, more convenient treatments represent a real improvement in the lived experience of people starting HIV today, compared to the ongoing struggles for many long-term treaters, who are now dealing with [experimental](#) [14] (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. agents, drug trials, or complicated treatments like T-20 (which needs to be administered by injection).

Side effects and long-term toxicities, of course, remain a crucial issue, particularly since so many people with HIV in Australia do have longer, more complicated treatment histories. Nonetheless, Australian doctors treating people with HIV have far more experience than ever before in preventing, treating, and alleviating side effects through the use of allied health services such as dieticians or exercise programs.

Much more is known about the specific causes of some side effects. While no HIV regimen at the moment is likely to be completely free of side effects, we now know more about things such as how to screen for and identify the risks (e.g. for renal problems, or hypersensitivity), how to put steps in place to minimise these risks, and how to manage side effects and toxicities which do occur.

For facial and limb fat wasting – for many people, the most distressing and feared of toxicities – studies are now taking place into agents such as uridine (a nucleoside ‘replacement’ supplement), and pravastatin, following promising results from small trials that suggest these agents may, over time, assist people to regain limb fat lost through HIV treatment. Other substances, such as magnesium orotate, are being investigated as potential candidates to alleviate or treat notoriously intractable problems like peripheral neuropathy (a kind of painful nerve damage).

There have, of course, been disappointments and frustrations. Many people were hoping that the large, international Strategies for the Management of Antiretroviral Therapy (SMART) study (reported on in the last edition of PL) might have shown that it was possible to effectively manage HIV disease progression and minimise the effects of drugs in the long term, by taking breaks from treatment using CD4 count as a guide to when to start or stop treating. SMART, as it turned out, showed the reverse was true – the most effective and safest strategy is to remain on antiviral treatment once you have started on it – with people experiencing many more health problems as a result of stop-starting treatment.

But there's an upside to this too, I think. The results of the SMART trial provide an even greater impetus for clinicians, researchers, and those involved in the care of people with HIV to make the most of the new opportunities we have – including new drugs, more tolerable combinations, clinical trials and the wealth of emerging information, to give some meaning to the ‘living’ part of ‘living with HIV’.

It might be ‘the virus, stupid’ – but the virus does not always have to be the last word.

- [bevirimat \(MPC-4326, PA-457\)](#)
- [darunavir](#)
- [entry and fusion inhibitors](#)
- [HIV treatments](#)
- [integrase inhibitors](#)
- [Lipodystrophy and lipoatrophy](#)
- [maturation inhibitors](#)
- [multi-class formulations](#)

Links:

- [1] <http://www.napwa.org.au/glossary/term/122>
- [2] <http://www.napwa.org.au/glossary/term/125>
- [3] <http://www.napwa.org.au/glossary/term/123>
- [4] <http://www.napwa.org.au/glossary/term/109>
- [5] <http://www.napwa.org.au/?q=taxonomy/term/447>
- [6] <http://www.napwa.org.au/glossary/term/91>
- [7] <http://www.napwa.org.au/glossary/term/92>
- [8] <http://www.napwa.org.au/taxonomy/term/240>
- [9] <http://www.napwa.org.au/glossary/term/124>
- [10] <http://www.napwa.org.au/taxonomy/term/296>
- [11] <http://www.napwa.org.au/glossary/term/112>
- [12] <http://www.napwa.org.au/taxonomy/term/202>
- [13] <http://www.napwa.org.au/glossary/term/492>
- [14] <http://www.napwa.org.au/glossary/term/491>