

## Smart moves

Created 15 Apr 2004 - 7:00am

We have more anti-HIV drugs than ever before. But do we really know the best and safest way to use them over the long term? KIRSTY MACHON reports.

Since the arrival of combination [antiviral](#) [1]A medication or substance which is active against one or more viruses. May include anti-HIV drugs, but these are more accurately termed antiretrovirals. treatments in the mid-1990s, there has been no shortage of edicts, theories, and fashions when it comes to the question of how best to use them to fight HIV.

In the initial burst of — understandable but misplaced — ‘protease optimism’ the now-famous treatment mantra was ‘hit hard, hit early’, the idea being to get people onto antiviral drugs as soon as possible — and then to keep them there indefinitely — in a bid to keep the [virus](#) [2]A small infective organism which is incapable of reproducing outside a host cell. at the lowest levels possible, preventing it from infecting more CD4 cells and causing immune damage or illness. ‘Compliance’ became the new buzzword. This was later, and somewhat grudgingly, changed to ‘adherence’, no doubt by worthy zealots ever-alert to the philosophical implications of language — but in practice, the two words carried the same daunting message: Keep taking the pills. Stop treatment and you could get sick and die.

Over the years that followed, the optimistic view that it was possible or even desirable to treat people as early as possible and keep them on treatments indefinitely, came up against some substantial challenges. The first was the nature of [combination therapy](#) [3]Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together. itself. It became increasingly clear that for many people, a lifetime defined by a metronomic daily round of pills was untenable.

Secondly — and profoundly more confronting for many — was the disturbing array of side effects and toxicities now beginning to show up over time: chronic diarrhoea, acute [liver](#) [4]A large organ, located in the upper right abdomen, which assists in digestion by metabolising carbohydrates, fats and proteins, stores vitamins and minerals, produces amino acids, bile and cholesterol, and removes toxins from the blood. failure, increased risk of heart disease, and the long-term body shape and metabolic changes loosely referred to as ‘lipodystrophy’.

A third challenge was the limitation of the drugs themselves as, over time, and in many cases despite rigorous adherence, many HIV positive people began to develop [resistance](#) [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 the pills. HIV, it seemed, was more wily and evasive than we thought, and it seemed there was a credibility gap emerging between the rhetoric and the reality of treatment.

The idea behind aggressive and early treatment is a simple one: control HIV and prevent it from replicating and destroying crucial CD4 immune cells, and you will stave off disease progression. It’s an intuitively sensible idea, summed up in a quote once used by David Ho, the mastermind behind the protease inhibitor, to open his presentation to the 1996 International AIDS Conference in Vancouver, Canada: “It’s the virus, stupid!”

In this philosophy, you take your cues for treatment decisions using [viral load](#) [6]A measurement of the quantity of HIV RNA in the blood. Viral load blood test results are expressed as the number of copies (of HIV) per milliliter of blood plasma. as the bottom line. ‘Undetectable’ viral load is the goal and the standard. If your viral load is detectable, or rising, you need to treat or change your treatments, according to this argument. Sometimes, the threshold is set with a little more leeway (a viral load of 10,000, for example, is sometimes considered to be the tipping point), but the rationale is the same: treat according to how much viral replication is occurring.

But as people began taking treatments over the longer term, a set of critical questions began to ferment. Treating hard and early is all very well, but it runs two very serious risks: one, that the patient will develop a long-term [side effect](#) [7]Any undesired actions or effects of a drug or treatment. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems. Experimental drugs must be evaluated for both immediate and long-term side effects. which could potentially be as dangerous as an opportunistic infection (or even fatal) and, two, that faced with the concept of a lifetime on pills, people may stop taking their drugs for

short or long periods of time for various reasons — and that they may do this with, or without, the consent of their doctor. This is what is usually meant by a ‘drug holiday’ or ‘treatments break’.

The language and science around this can be quite confusing. Stopping pills due to side effects or for personal reasons (such as ‘cleaning out my system’) is a different thing altogether from a Strategic Treatment Interruption — based on the idea that by stopping treatment you may be able to encourage your immune system to ‘kick back in’ and begin to control HIV on its own. There has been very limited evidence to date that this actually happens — and there is no evidence for it at all in people who had HIV for more than six months before they took their first treatments.

Most people who stop treatment, however, are not doing so because they are labouring under the misapprehension it will boost their autoimmunity against HIV: they are doing it for other reasons altogether.

As HIV-positive people began, for various reasons, to take periodic breaks from treatments in larger numbers, it became clear that taking time off pills did not always lead to rapid loss of CD4 cells or opportunistic illness. In addition, the phenomenon of treatment breaks raised an important question about how to use HIV treatments realistically. Researchers began to wonder whether, given the very real risk of potential toxicities or ‘treatment fatigue’, it was better to delay starting treatments until they were really needed, using CD4 count rather than viral load as the guide.

This idea has already been reflected in changes to international treatment guidelines, which now generally recommend that treatment be deferred until the CD4 count falls to as low as 350 or even 250, when the risk of opportunistic infection is very real. There is no evidence that people are at significant risk of developing opportunistic infections with CD4 counts of, say, between 350 and 500 — although 500 CD4 cells had once been considered the ‘safety threshold’ for starting treatments. Moreover, there is some evidence that when many people restart treatment even with low CD4 cells, they begin to gain back cells over time once viral replication is controlled again — although this can be a slow process, and in some cases, CD4 counts will remain stubbornly low despite reintroducing treatment.

Putting all this information together is complicated. There are many ‘ifs’ and ‘buts’, and the frustrating fact remains that HIV can behave entirely differently in individual people, even if they appear to be in similar situations.

Researchers now believe that there is a need for strategic research to answer some big, long-term questions about how to best use the anti-HIV drugs we have. One of these studies is the so-called SMART study (Strategies for Management of Anti-Retroviral Therapy).

SMART is designed to compare, over a long period of time, two important possible strategies for treating HIV. Participants in this study will be randomly assigned to one of two groups, or ‘arms’. The first group is treated according to a strategy of total viral suppression. This might be called the “it’s the virus, stupid” arm. People in this arm of the study are treated with the goal of keeping HIV at undetectable levels. If viral load becomes detectable, treatment will be modified in order to maximise the likelihood of keeping viral load levels as low as possible at all times.

The second arm of the study is aimed at conserving the use of antiviral drugs until they are most needed, using CD4 count and risk of opportunistic infection as the guide. In this arm, [antiretroviral](#) [8]A medication or other substance which is active against retroviruses such as HIV. treatment is not started until a person has a CD4 count of fewer than 250 cells. If the CD4 count is 350 cells or more on two consecutive occasions at least two months apart, treatment will be stopped.

The idea of SMART is that, over a long period of time and in a careful and controlled way, researchers will be able to compare people in both arms of the study for several outcomes, to see if there are any differences. Importantly, the study looks at quality of life as well as medical outcomes.

There are potential risks as well as possible benefits for both arms. Obviously, the longer you are on treatments aimed at minimising viral load, the greater your exposure to the drugs over time. It remains to be seen if this therefore increases the risk of side effects or significant toxicity, but that is clearly one risk of this strategy.

Deferring treatment also has potential hazards. Although opportunistic infections don’t tend to occur much above 250 CD4 cells, substantially less is known about other kinds of damage which can occur as a result of HIV.

Neurological problems such as early dementia and some cancers, for example, can potentially occur when CD4 cells are somewhat higher than most OIs, and less is known about precisely when and how they are triggered. So being off treatment could theoretically be a problem for this group of conditions, although all patients are carefully monitored.

The study will try to determine whether there is any difference in how long people survive without developing HIV complications like opportunistic infections; their ability or capacity to adhere to treatments; side effects including metabolic problems like [diabetes](#) [9][Diabetes mellitus] A disorder in which sugars in the diet cannot be metabolised into energy due to a lack of the enzyme insulin. Late-onset diabetes mellitus may be a long-term side effect of some anti-HIV drugs., high [cholesterol](#) [10]An essential component of cell membranes and nerve fibre insulation, cholesterol is important for the metabolism and transport of fatty acids and the production of hormones and Vitamin D. Cholesterol is manufactured by the liver, and is also present in certain foods. High blood cholesterol levels have been linked to heart disease and may be a side effect of some anti-HIV medications. or lipodystrophy; quality of life; and development of resistance to their HIV treatments.

SMART is taking place in 22 countries around the world, including sites across Australia. People [enrolling](#) [11]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. in the study are expected to be followed for an average of about 7.5 years — for many people, this is a somewhat daunting prospect.

The SMART study sets out to ask some very important questions, which may clarify a lot of the unknowns about the best way to manage HIV. It's a [randomised](#) [12]A method based on chance by which study participants are assigned to a treatment group. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms. The researchers do not know which treatment is better. From what is known at the time, any one of the treatments chosen could be of benefit to the participant study, so people have no choice as to which arm they are allocated into. For this reason, it will not be for all patients, particularly if you or your doctor may want to be able to exercise more immediate and direct control over your treatment strategies. However, it does present an opportunity to participate in a project which has a bigger picture in mind — and researchers hope it is able to provide some reliable answers about a fundamentally important question: what's the best way to use the drugs we have?

- [clinical trials](#)
- [HIV treatments](#)

#### Links:

[1] <http://www.napwa.org.au/glossary/term/123>

[2] <http://www.napwa.org.au/glossary/term/125>

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

[4] <http://www.napwa.org.au/glossary/term/102>

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

[6] <http://www.napwa.org.au/glossary/term/416>

[7] <http://www.napwa.org.au/glossary/term/471>

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

[9] <http://www.napwa.org.au/glossary/term/95>

[10] <http://www.napwa.org.au/glossary/term/88>

[11] <http://www.napwa.org.au/glossary/term/489>

[12] <http://www.napwa.org.au/glossary/term/513>