
The magic number: research points to the right time to start treatment

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The evolution of HIV medicine over the last quarter century has led to answers for many of the big questions about how to treat people living with HIV. In 2007, we know that using multiple drugs from different classes, maintaining adherence to dosing schedules and being responsive to side effects and toxicities are all key parts of the broad response to HIV.

But there is one important question we still don't have an answer for, or at least not a single answer that clinicians and researchers universally agree on: what is the right time to begin treatment?

Fortunately, a consensus is starting to emerge, and while there have been some false starts in the past, it looks like this time we may be on the right track. In a nutshell, the 'magic number' is 350 – that's the CD4 count at which it seems HIV treatment should be commenced – but there's more to it than just one number.

Determining the best time to start treatment has been a major focus of HIV research for more than a decade, ever since (and indeed before) the advent of Highly Active Antiretroviral Therapy ([HAART](#) [1] Highly Active AntiRetroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together.). At first we had the 'hit hard, hit early' approach, based on the hope that by aggressively treating HIV at the first available opportunity, it might be possible to completely eradicate it from the body. That turned out to be an overly optimistic goal, as it became apparent that the [virus](#) [2] A small infective organism which is incapable of reproducing outside a host cell. would rebound once treatment was withdrawn.

The 'hit hard, hit early' approach lingered for several years, until the late 1990s, when the emergence of long-term toxicities such as lipodystrophy, [diabetes](#) [3] [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. and increased heart disease risk led to a re-evaluation, and a move away from early treatment. If HIV couldn't be eradicated, people would have to be maintained on treatments for many years, and obviously the impact of long-term toxicities would only get worse with more time on treatment. So around the turn of the century, most doctors abandoned early treatment and advised their patients to delay starting on HAART until their CD4 counts had fallen to a lower level.

There wasn't immediately a great deal of consensus about what that 'lower level' should be, with some doctors advocating delaying treatment for as long as possible – perhaps until the CD4 count gets down to about 200 – and others recommending treatment start when the patient's CD4 count gets down to 300 or 350.

In Australia, the [Pharmaceutical Benefits Scheme](#) [4] [Pharmaceutical Benefits Scheme] The federal government program which subsidises medication costs in Australia. Anti-HIV drugs are part of a special part of the PBS called Section 100 (S100) which is used for expensive, highly specialised drugs. rules for prescribing HIV medications typically specify that these drugs can be prescribed to people with CD4 counts below 500, but Australian doctors predominantly follow the guidelines produced and updated annually by the Australasian Society for HIV Medicine (

So, from the early days of 'hit hard, hit early', the pendulum swung back to a much more conservative approach , delaying treatment until the CD4 count falls to as low as 200, below which the risk of developing HIV-related illnesses starts to climb. Now it appears the pendulum is swinging again.

In an article in the British Medical Journal in January*, a group of eminent HIV physicians argue that current prescribing guidelines for UK doctors should be revised to recommend starting treatment at the 350 mark. The UK guidelines are broadly in line with their Australian and US counterparts, saying that treatment should be considered once the CD4 count falls below 350, but is only "strongly recommended" once it falls below 250.

"Antiretroviral therapy clearly reduces the risk of AIDS related diseases, even in those with a relatively high CD4 count," the authors write, "so what have been the reasons for delaying?"

The article examines the three main justifications for delaying treatment and finds, in each case, good reasons to start treatment a little earlier.

Firstly, there is the issue of side effects and toxicities: these range from the merely unpleasant (diarrhoea, nausea, headache, etc) to serious but fortunately rare events such as hypersensitivity reactions, lactic acidosis and pancreatitis. Added to this, there is evidence that long-term antiretroviral therapy increases the risk of lipodystrophy, heart disease and a range of other serious illnesses.

The authors argue that our understanding of and ability to manage these complications has improved in recent years – in the case of lipodystrophy, for example, we now know that this is related to the use of a small subset of [antiretrovirals](#) [7] A medication or other substance which is active against retroviruses such as HIV., particularly d4T, which is no longer in widespread use. Likewise, the increase in risk of [heart attack](#) [8] A life-threatening emergency in which the blood supply to the heart is suddenly cut off, causing the heart muscle (myocardium) to die from lack of oxygen. has been shown to be associated with protease inhibitors and not non-nucleosides, and can be partly offset by managing other risk factors like high [cholesterol](#) [9] 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. and triglycerides, smoking and diet.

Furthermore, the article points to evidence from the SMART and DAD studies which suggest higher rates of some adverse events in people who are not on treatment or who take treatment intermittently. The DAD study has recently found an increased risk of death from [liver](#) [10] 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. disease and 'non-AIDS' cancers among people with lower CD4 counts.

Secondly, the authors point out that the decision to delay treatment is justified by the relatively low risk of HIV disease progression in people with CD4 counts above 250. For example, a 35-year-old with a CD4 count of 350 and viral load of 30,000 has a 1.6 percent risk of developing an AIDS-defining condition within six months, according to the authors. "While this risk would be reduced by antiretroviral therapy, many clinicians and patients have not considered it sufficiently high to warrant initiation of therapy," they write.

While the risk of disease progression for a given CD4 count has not changed with newer treatments, "the context in which we are weighing up the risk has altered." Treatments have evolved to the point where many HIV-positive people can expect to have a relatively normal lifespan, and when seen in that context a 1.6 percent risk of developing AIDS within six months (in the example above) "begins to not look so low." The authors point to recent


A third reason for delaying treatment is the idea that newer, better and more tolerable HIV treatments could be coming along, and it could make sense to wait until these become available if there is no great urgency to treat now. The example is given of a patient starting treatment in 1996, who "might have been put on a regimen containing either full-dose ritonavir (associated with severe gastrointestinal adverse effects) or hard gel saquinavir (associated with a high rate of [resistance](#) [12] HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant.). If he or she had been able to wait until 1999 then a regimen of Combivir and efavirenz could have been started, which has proved durable success and is still widely used."

The idea that newer, better treatments might come along soon enough, or that toxicities from existing treatments are yet to be uncovered, is one that has a strong resonance in our community and can act as a disincentive for starting treatment. But, say the authors, recent clinical trials have shown a tendency towards a plateau in the [efficacy](#) [13] (Of a drug or treatment). The maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the standard procedure, Phase II clinical trials gauge efficacy, and Phase III trials confirm it. of anti-HIV treatments, with new drugs struggling to demonstrate improved efficacy over existing treatments. "Viral load responses are now generally so good that there may be little scope for further improvement," they write. Indeed, the focus of much antiretroviral development in recent years has shifted towards the development of drugs for 'third-line' and 'salvage' regimens, and so there is little likelihood of significant change in first-line therapies in the foreseeable future.

"Delaying treatment until the CD4 count has fallen below 300–350 carries risks that it seems will not be balanced

[start treatment](http://www.napwa.org.au/pl/2007/03/the-magic-number-research-points-to-the-right-time-to-start-treatment),
or outweighed by any short or longer term mortality risks from immediate therapy,” the authors conclude. “We therefore suggest that treatment guidelines should recommend starting treatment at about 350, so long as the patient is ready.”

For the time being, the Australian guidelines for starting anti-HIV treatment are unchanged, and as always the decision to begin treatment is one that each individual will have to take for him or herself. We probably still have some way to go before there is universal agreement about the best time to start treatment, but it seems a fair guess that a CD4 count of 350, or thereabouts, is where we’re headed.

Attachment	Size	Type
Phillips AN et al. ‘When should antiretroviral therapy for HIV be started?’, BMJ 2007;334:76–78 [14]	395.1 KB	 PDF

- [starting treatments](#)

Links:

- [1] <http://www.napwa.org.au/glossary/term/96>
- [2] <http://www.napwa.org.au/glossary/term/125>
- [3] <http://www.napwa.org.au/glossary/term/95>
- [4] <http://www.napwa.org.au/glossary/term/121>
- [5] <http://www.napwa.org.au/glossary/term/382>
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