

## Viral rebound: How stop-start spelled the end for SMART

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The sudden cancellation of a large HIV [clinical study](#) [1] A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed. has significant implications for how we treat HIV.

Taking a break from HIV treatments can appreciably increase your risk of developing an AIDS-related condition, experiencing serious health problems, or even dying, a large international [randomised](#) [2] 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 comparing continuous treatment to intermittent therapy has concluded.

The SMART (Strategies for Management of [Antiretroviral](#) [3] A medication or other substance which is active against retroviruses such as HIV. Therapy) study set out to compare two different approaches to HIV treatment – continuous antiviral therapy, aimed at keeping [viral load](#) [4] 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. low, versus intermittent treatment with breaks when CD4 counts rose above set levels.

Although the majority of people in both arms of the study remained well, researchers were forced to halt enrolment into the landmark trial in January when it emerged that substantially more people died, developed AIDS, or suffered serious health issues following treatment interruptions guided by CD4 count, compared to those who remained on continuous antiviral therapy.

But while SMART researchers say that the study question has been answered – remaining on treatments once you've started them is a less risky strategy than stop-starting according to your CD4 count – the surprise results have raised some important questions.

Of particular interest was the fact that, contrary to what many expected, reducing exposure to antiviral treatment by taking breaks did not, in this trial, reduce the risk of developing problems associated with long-term exposure to antiretroviral drugs, such as cardiovascular disease, kidney toxicities and [liver](#) [5] 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. problems. In fact, quite the opposite occurred: people who interrupted treatment ended up being more likely to suffer from these problems. This has led some to hypothesise that the body's immunological and virological responses to periodically going on and off treatment might themselves pose a risk.

Typically, when a person comes off treatment, the virus begins to replicate and their CD4 cell count drops fairly quickly. Tied to this are complex inflammatory and immune system responses, and some people believe that these processes themselves may lead to an increased risk of some of the adverse outcomes observed in SMART.

### Interpreting the study

SMART, which was conducted in over 30 countries, compared two treatment strategies. At the time enrolment was stopped, 5472 people had been randomised into the study. In the Viral Suppression arm, people were required to take antiretroviral treatments continuously for the duration of the study, with the aim of keeping HIV as fully suppressed or controlled as possible. In the Drug Conservation arm, participants would cease antiviral treatment once their CD4 count had been sustained at 350 cells/mm<sup>3</sup> or above for a 2-3 month period, then resume treatment if they dropped to less than 250 cells (below which the risk of disease progression is considered high).

(To avoid confusion, in this article the two arms are referred to as 'continuous treatment' and 'intermittent treatment', rather than 'Viral Suppression' and 'Drug Conservation', the terminology used by the researchers.)

SMART intended to explore, among other things, whether using antiviral drugs only at the times when an individual was most at risk of HIV disease progression (defined by CD4 cell count) would, over a long period of time (6-9 years) be no less effective a strategy for managing HIV infection than using the available drugs continuously. In addition, the study examined whether conserving the use of [antivirals](#) [6] A medication or substance which is active against one or more viruses. May include anti-HIV drugs, but these are more accurately termed antiretrovirals. In this way would reduce some of the toxicities and side effects of treatment.

In January 2006, however, the study's [Data Safety and Monitoring Board](#) [7] An independent committee, composed of community representatives and clinical research experts, that reviews data while a clinical trial is in progress to ensure that participants are not exposed to undue risk. A DSMB may recommend that a trial be stopped if there are safety concerns or if the trial objectives have been achieved. (which keeps track of the study to ensure it is safe or ethical to continue) had to deal with some worrying news. It was revealed that 93 people in the intermittent treatment arm had died or developed an AIDS-related condition, compared to 44 people in the continuous treatment arm.

In nearly half of these events, the participants had died (47 deaths were recorded in the intermittent treatment arm, and 27 in the continuous treatment arm), with oesophageal candidiasis (thrush in the gullet and throat) being the second most commonly reported serious event. In other words, there was roughly a doubling of the risk for people who interrupted treatment.

It should also be noted that not all deaths were related to AIDS or HIV treatment toxicity. In both arms, there were a small number of deaths from violent or accidental causes. However, the number of these deaths was the same in each arm, so the statistical difference in deaths related to AIDS between each arm does remain real.

One important and under-reported aspect of these results is that, overall, the numbers of people who developed AIDS or died on the study was actually very small, in the context of the five-and-a-half thousand people [enrolled](#) [8]

The results pose some other perplexing challenges to prevailing wisdom. For example, the risk of developing AIDS and opportunistic illness is well known to increase as CD4 count decreases. But in SMART, neither the number of CD4 cells a person had on entering the study nor their lowest-ever CD4 cell count (nadir) made a difference to their likelihood of developing an AIDS-related condition or adverse event. Regardless of CD4 count, it was stopping treatment which was associated with an increased risk of disease progression.

Furthermore, people who entered the study while taking antiretroviral therapy were three-and-half times more likely to experience an adverse health event if they had undetectable viral load, compared to someone on treatment but with detectable viral load.

The SMART results certainly show that rapid loss of CD4 cells can occur on stopping treatment, something researchers anticipated based on anecdote and other [clinical](#) [9] Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. studies. When people stopped antiviral treatment after being randomised to the intermittent treatment arm, there was an average decrease of about 173 CD4 cells in the first month after stopping. After the initial drop, CD4 cells continued to decline, though much more slowly, on average by about four cells per month.

## What about toxicities?

When SMART was first designed, it was anticipated that there would be demonstrable risks associated with stopping treatment for periods of time. One of the hopes was that the study might show that this was compensated, or 'made up for', by reduced treatments-related toxicity among people taking breaks. Frustratingly, this seems not to have been the case – and this was one of the reasons that the study was stopped. SMART looked at many of the adverse events and problems often attributed to HIV treatments, such as metabolic complications (like blood sugar problems or [artery](#) [10] a blood vessel which carries oxygenated blood away from the heart.) disease, pancreatitis, lactic acidosis, and liver or kidney failure.

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There was no toxicity [endpoint](#) [11] Overall outcome that a clinical trial protocol is designed to evaluate. Common endpoints are severe toxicity, disease progression, or death. where people randomised to treatment interruption had a better outcome than those who stayed on antivirals. For virtually all conditions, there was a higher risk of developing treatment toxicities in the treatment interruption group. In other words, stopping treatment actually increased the risk of potentially life-threatening treatment toxicities.

## What's the explanation for all of this?

Presenting the results of SMART at the Denver conference on Retroviruses and Opportunistic Infections, researcher Wafaa El-Sadr noted that one explanation for the differences could be linked to increased levels of inflammation and immune system activation which can occur when viral load or CD4 levels fluctuate or change rapidly.

Overall, people in the study who interrupted treatment spent longer periods of time with lower CD4 counts, and were more likely to experience fluctuating levels of virus, as they stop-started antiviral treatment. Chronic inflammatory action in the body is known to be a risk factor for cardiovascular disease anyway – and this may explain in particular why cardiovascular complications were not reduced just by stopping treatment, El-Sadr told the conference.

## Is this the end for drug holidays?

The clear implication of the SMART outcome is that once you start taking HIV antiviral treatment, it's best and safest to remain on treatment. This has been characterised by some as 'antiviral treatment is for life', and it's pretty obvious from SMART that treatment breaks shouldn't be considered an equivalent 'management strategy' to continuous treatment, since there is appreciable risk you'll do worse in the long term. The idea that treatment breaks are a form of 'detoxification' from antiviral treatments, for example, or that the health outcomes are the same as staying on treatment, is clearly not borne out by SMART.

On the other hand, the reasons why people stop taking HIV treatments are many and varied, and the evidence from SMART as well as our cumulative experience of antiviral therapy is that many people can and do stop treatment for periods of time without suffering immediately catastrophic results or illness. However, SMART has shown us that the risks are very real and quantifiable, and this needs to be well understood.

One thing SMART definitely points to is the ongoing need to be proactive in finding combinations of drugs that are tolerable, easy to take, and with minimal side effects. If you're considering taking a treatment break due to tolerability problems with your current combination, it would be prudent to first of all see whether there is a different combination you could switch to with a better side effect profile, allowing you to stay on treatment. If you're on your first drug combination with well-controlled viral load, a good CD4 count, and several new drugs around to choose from, this choice will be particularly important – so that you can remain on treatment, and preserve the advantage you have, and minimise the particular risks associated with stopping treatment if your viral load is low.

It also suggests that if you're starting treatment for the first time, you should be prepared to stick with it – and you should expect the support of your doctor in helping you choose a realistic drug combination that you're able to live with.

It's expected that participants in SMART will be followed up in some way, at least in the short term. Investigators have been advised that those people randomised to treatment interruptions should be advised to go back onto treatments. Meanwhile, the data-and-numbers crunching continues, as researchers look further into this perhaps disappointing, but compelling, result.

## Breaking the rules? Studies leave some experts perplexed, divided

SMART was not the only study on treatment interruptions to be presented at the 13th Conference on Retroviruses and Opportunistic Infections in February. Several other studies were also presented looking at various treatment break strategies. SMART was by far the largest, and because of its design, the results widely considered to be the most applicable and robust. But a panel discussion on the issues raised heard that further work was needed to

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understand the implications of different studies and approaches, especially since, in the words of one New York-based HIV treatments advocate, “the assumption that most people are going to be on therapy for the rest of their lives is not a practical assumption.”

### Against treatment breaks

- A French study called Trivican, being conducted in the Ivory Coast in Africa, examined fixed length treatment interruption (two months on, two months off), guided by CD4 count (as with SMART), compared with continuous treatment. There were 840 participants. The treatment interruption arm was stopped early, due to significantly more serious illness occurring in this arm.

### Hedging their bets

- A second French study, the Window study, examined a complex strategy using treatment interruptions of increasing length, in people experienced in antiviral therapy, compared to remaining on treatment. With a sample size of 391, it was significantly smaller than SMART, and its endpoint was not clinical progression to illness or death, but the number of people whose CD4 counts fell below 300. By this definition, the treatment interruption arm was declared ‘non-inferior’ – a technical term which essentially means that although the study couldn’t conclude that the two strategies were equal, nor was there enough difference between the two arms to argue that staying on therapy was definitely a better approach.
- An Italian study, using a similarly complex pattern of treatment interruption also found this to be ‘non-inferior’ to continuous therapy. This was a smaller study again (273 people) and its endpoint was, again, not clinical progression to illness or death, but the proportion of people who retained more than 500 CD4 cells. In addition, this study group had overall much higher CD4 counts on entering the study. There was little major illness or death seen in this study, but the caution is that this was a very different group of people to the SMART study.

- [clinical trials](#)
- [treatment interruption](#)
- [treatment side effects](#)

### Links:

- [1] <http://www.napwa.org.au/glossary/term/89>
- [2] <http://www.napwa.org.au/glossary/term/513>
- [3] <http://www.napwa.org.au/glossary/term/122>
- [4] <http://www.napwa.org.au/glossary/term/416>
- [5] <http://www.napwa.org.au/glossary/term/102>
- [6] <http://www.napwa.org.au/glossary/term/123>
- [7] <http://www.napwa.org.au/glossary/term/481>
- [8] <http://www.napwa.org.au/glossary/term/489>
- [9] <http://www.napwa.org.au/glossary/term/475>
- [10] <http://www.napwa.org.au/glossary/term/83>
- [11] <http://www.napwa.org.au/glossary/term/488>