factsheet 51
revised may 2006

treatment interruptions

This factsheet has been revised because of the recent premature termination of a large study examining the safety of structured treatment interruptions and the discontinuation of the treatment interruption arm of another large study. It explains the background to these studies, why they were stopped, and their possible implications.

The SMART study

The SMART (Strategies for the Management of Antiretroviral Therapy) study recruited people taking anti-HIV treatment with a CD4 cell count above 350 cells/mm^3. Patients were randomised into one of two treatment arms: the first continued to take anti-HIV therapy as normal, the other stopped treatment, restarting when their CD4 cell count fell to around 250 cells/mm^3 (the point where people start to become more vulnerable to serious infections), and then stopping again when their CD4 cell count once again reached 350 cells/mm^3 and so on. Among other things, the researchers wanted to see if people taking treatment breaks remained well, and how many avoided the side-effects of anti-HIV drugs.

However, in January 2006 the study was stopped early because 4% of people who interrupted their anti-HIV treatment experienced disease progression compared to only 2% of people who took their HIV drugs all the time. Although there is not much difference in these absolute rates, the difference was highly statistically significant, and the researchers estimated that those taking treatment breaks were more than twice as likely to become ill or die than those taking continuous HIV treatment.

As well as an increased risk of HIV disease progression, people taking treatment breaks also had an increased risk of adverse events such as cardiovascular disease, and kidney or liver disease. This was a surprise, as these conditions can be side-effects of anti-HIV treatment and the study's researchers expected to see more of these illnesses in people taking HIV treatment all the time.

It is thought that a reason why people taking treatment breaks experienced more illness was because they spent more time with low CD4 cell counts, increasing the risk of HIV disease progression.

The DART study

Shortly after the SMART study was stopped, the treatment interruption arm of another study was also terminated (although the main aspect of the study looking at the monitoring of HIV disease progression will continue). Researchers were looking at fixed cycles of anti-HIV treatment in people who had achieved a CD4 cell count of 300 or more. In the DART (Development of Anti-Retroviral Therapy in Africa) study people with a CD4 cell count of over 300 were randomised to either receive continuous HIV treatment or to take twelve-week cycles of HIV treatment followed by twelve-week breaks. However, the treatment interruption arm of the study was stopped early and all patients advised to switch to continuous treatment when the researchers noticed that people in the treatment cycle arm were more likely to develop HIV-related illnesses.

All the people in the treatment interruption study had a CD4 cell count above 300 cells/mm^3 when they entered it, but many had had a low CD4 cell count before starting HIV treatment and the DART doctors concluded that twelve week cycles of treatment followed by interruptions were unsafe for people who started HIV treatment with a CD4 cell count below 200 cells/mm^3 or a history HIV related illness.

Implications

Treatment interruptions initially became a hot topic amongst HIV researchers after a handful of people who had previously taken anti-HIV treatment maintained a very low viral load even when they stopped treatment. However, larger trials failed to find any benefit from stopping treatment.

Attention then turned to the value of treatment breaks guided by CD4 cell count. The SMART study has shown that there are also concerns about the safety of this approach. Specifically, what SMART and DART showed was that although many people can interrupt HIV therapy without any harm, CD4 guided or fixed-cycle treatment interruptions have risks in people with previous experience of anti-HIV treatment. There are ongoing studies looking at treatment interruptions at the time of primary infection and in children, and it is still possible that future studies will look at treatment interruptions in other groups of people who have never taken HIV drugs before.

The reasons why people may want to consider a treatment break also still remain: taking anti-HIV treatment appears to need life-long commitment with the currently available drugs. What's more, it is essential to take at least 95% of the doses of HIV treatment at the right time and in the right way for them to work effectively and to avoid HIV becoming resistant to them. Many people find this daunting or impossible.

The side-effects of anti-HIV treatment are also a big concern. In particular, it is known that longer-term anti-HIV treatment can cause side-effects such as changes in body fat distribution and increases in levels of blood fats (lipodystrophy), which can lead to an increased risk of heart disease and stroke. It had been hoped that limiting the amount of time a person spent on HIV treatment would be a way of reducing the risk of these developing.

If you are thinking of taking a break from your anti-HIV drugs speak to your doctor about how advisable and safe it is for you to do so, and if you are currently taking a break from treatment make sure that you go to your HIV clinic regularly to have your CD4 cell count, viral load and health closely monitored.

Potential hazards of treatment interruptions:

- Rising viral load and falling CD4 could present a risk of infections or other illness.
- Though many people regain lost CD4 cells and re-suppress their viral load once treatment is re-started, these may not fully return to the levels achieved before the interruption.
- Some people experience flu-like symptoms during a rebound in viral load.
- The rebound in viral load could re-seed viral reservoirs which had been diminished by treatment.
- Anti-HIV drugs differ in the speed at which they leave the body, and these uneven, low drug levels can result in drug resistance. It may be unsafe to stop some drug combinations abruptly, particularly those that include efavirenz or nevirapine. Seek your doctor's advice on the drug combination you are taking.
- Rather than improving quality of life, cycling on and off treatment may reduce it. The 'habit' of adherence may need to be re-learnt, and side-effects may need to be re-endured with each interruption.
- There have been cases of people being superinfected (or reinfected) with a different strain of HIV whilst taking a treatment break.

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