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Should you continue or stop your treatment for HIV infection?

The long-term side effects of HIV treatment have become a source of concern for many HIV+ individuals. They have even dampened initial enthusiasm sparked by the introduction of effective triple therapies in the mid-1990s. We now know that HIV treatment does not eliminate the virus from the body. Treatment must be continued indefinitely. However, many people living with HIV are tempted to interrupt their treatment, even if their immune system has improved significantly and their viral load has been undetectable for a long time.

Interrupting treatment provides a break and, in some cases, helps to control the unpleasant side effects of the therapy.

Before deciding whether or not to interrupt treatment, you should first find out about the potential benefits and drawbacks. In this document, I invite you to review the data from the numerous studies on so called *structured treatment interruptions*. These studies discuss the pros and cons of such a strategy and will help you make a more informed decision.

Treatment interruptions are studied based on three hypotheses:

1. Can short treatment interruptions strengthen the immune system?

Treatment makes the virus undetectable in the blood and prevents the immune system from actively reacting against the virus. When treatment is stopped, the virus reappears in the blood and becomes detectable within a few days or a few weeks. Researchers carried out a number of planned treatment interruptions of a few weeks' duration followed by resumption of treatment. They hoped to stimulate immune defenses against the virus and see whether the interruptions acted as a vaccine by strengthening the immune system against the virus. Unfortunately, this enticing theory proved false. Only a few patients who had been treated very early (within a few days) after contracting the virus saw their immune system strengthened after the interruptions. Some were able to go without treatment for several months[1].

In many patients treated during the chronic phase (i.e. several weeks, months or years after contracting the virus), the immune system did not react favourably to treatment interruptions[2,3]. The viral load (the number of viruses per millilitre of blood plasma) climbed back to the pretreatment level, and the drop in the CD4 immune cell count resumed, with harmful consequences on the health of some individuals.

2. Can you reverse resistance to treatment by stopping it for a certain amount of time?

The treatment you are being given may become ineffective in fighting a virus due to genetic mutations of the virus. This is known as *resistance*. The mutations can be detected in the blood through a resistance test. This test is ordered when a treatment no longer makes the viral load undetectable. When a treatment that is no longer working is stopped, the genetic mutations that caused the drug resistance usually disappear within a few weeks. Could this make the treatments effective again?

An important study has recently shown that a treatment interruption did not make the next treatment more effective[4]. The resistance that disappears when treatment is stopped seems to return in force as soon as a new treatment is started. During a treatment interruption, the virus can cause harm to the immune system, and complications of AIDS can occur.

However, another study seems to show the opposite[5]. A new treatment consisting of eight or nine medications (called *mega-HAART*) was more effective if administered after a 2-month interruption rather than immediately after the failing treatment.

The conclusions of these two studies seem contradictory. For now, treatment interruption after failure remains an experimental approach.

3. Can side effects and costs be reduced with long treatment interruptions, and how long should the breaks be?

This hypothesis is easy to understand. If treatment is stopped, the total duration of treatment is reduced. The side effects and costs of treatment are reduced as well. But what are the benefits and risks of such an approach?

A number of studies have looked at this. They involved interrupting treatment for a relatively long period of time, and then restarting treatment. The following were investigated, among others:

- Treatment interruptions and restart of fixed duration, such as treatment administered every other week or two months out of three[6].
- Treatment interruptions and restart of varying lengths depending on the CD4 immune cell count or the viral load. If the CD4 cell count falls too much (for example, below 350), the treatment is restarted. When it rises above a predetermined level (for example, above 500), the treatment is stopped again.

In general, it can be concluded that the CD4 cell count rises less with treatment interruptions than without. Short interruptions (one week) are not very effective and do not reduce the side effects. In the studies in which the treatment interruptions and restart were driven by the CD4 immune cell count, the total duration of treatment was reduced by about 50%, and some side effects were effectively controlled[7].

However, two major problems have been observed in treatment interruption studies:

- There were a few cases of drug resistance during the interruption period[8,9].
- In addition, about 3 to 10% of the people who stopped the treatment experienced symptoms of primary infection[10], i.e. the symptoms a person can develop upon contracting the HIV virus for the first time: fever, sore throat, lymph node swelling and skin rashes. These flu-like symptoms

disappear within a few weeks. They result from the rapid increase in the number of viruses in the blood (viral load) and their massive attack on the immune system.

Treatment interruptions seem safer in one specific patient population. It was observed that the "lifetime lowest" immune cell count (referred to as the *nadir*) determines how the body reacts to treatment interruption[11]. Individuals who have had a CD4 count below 200 will experience accelerated immune system weakening upon stopping their treatment. Those whose CD4 count has always been greater than 350 can stop their treatment for an average of more than one year without having to resume it[12,13,14]. A patient must nonetheless have enough CD4 cells to tolerate a certain amount of immune system weakening during the treatment interruption.

In conclusion:

Can the immune system be strengthened with short treatment interruptions?

No, except in rare cases.

Can you reverse resistance to treatment by stopping it for a certain amount of time?

We do not know; the results of studies are contradictory.

Can side effects and costs be reduced with treatment interruptions?

Yes, but there may be certain consequences, such as a reappearance of certain symptoms caused by the HIV, immune system weakening, or resistance. Individuals in the best position to stop their treatment for long periods of time are those who were treated before their immune systems were excessively weakened by HIV infection. Certain risks need to be assessed before treatment is stopped.

Treatment interruptions should be carefully planned. We do not have enough information to confidently state the long-term benefits and drawbacks of these strategies. Research in this area is very active, and studies are underway in Canada. You should be well informed and consult your doctor before making a decision. Remember that, for most people who are treated, the benefits of therapy are much greater than the drawbacks.

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Can I stop my treatment?

It is difficult to know who will benefit from treatment interruption. However, some things are clear:

- If you want to stop your treatment, first consult your doctor who can explain the benefits and risks that this strategy could have for you.
- You should take your medical history into consideration. Certain conditions have been associated with a higher risk of rapid immune system weakening during treatment interruptions. Examples:
  - If your CD4 immune cell count had previously been below 200.
  - If you had a high viral load (e.g. more than 100,000 copies per millilitre of blood) before you started treatment.
  - If you had previously developed signs of AIDS (i.e. an opportunistic infection or Kaposi's sarcoma), stopping your treatment could promote the recurrence of these complications.
- Precautions should be taken when stopping certain medications. Generally speaking, all triple therapy drugs should be stopped at the same time. However, some drugs stay in the blood longer than others. In some cases, they should be stopped a few days before the others. This will ensure that they are not acting alone against the virus for a few days, a situation that would enable the virus to adapt to these drugs and become resistant.
- Drugs for the prevention of opportunistic infections should also be prescribed when the immune system is excessively weak. You should not stop taking these drugs without first consulting your doctor.
- During a treatment interruption, you should monitor your health closely and have your CD4 immune cell count and viral load measured on a regular basis.
- Before stopping your treatment, plan with your doctor at what point you will restart it: Why stop the treatment, and why restart it? Should you plan on an interruption of fixed duration? Should your decision to resume treatment be based on your CD4 immune cell count or your viral load?
- If you stop your treatment because of side effects, also examine the other options, such as switching to another treatment and treating the side effects.
- Remember that during a treatment interruption, there are more viruses in the blood, semen and vaginal secretions. It is therefore easier to transmit HIV infection during unprotected sexual relations or when sharing syringes. However, the usual means of protection (using a condom and not sharing drug equipment) are equally effective in reducing the transmission of the virus during treatment interruption.

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