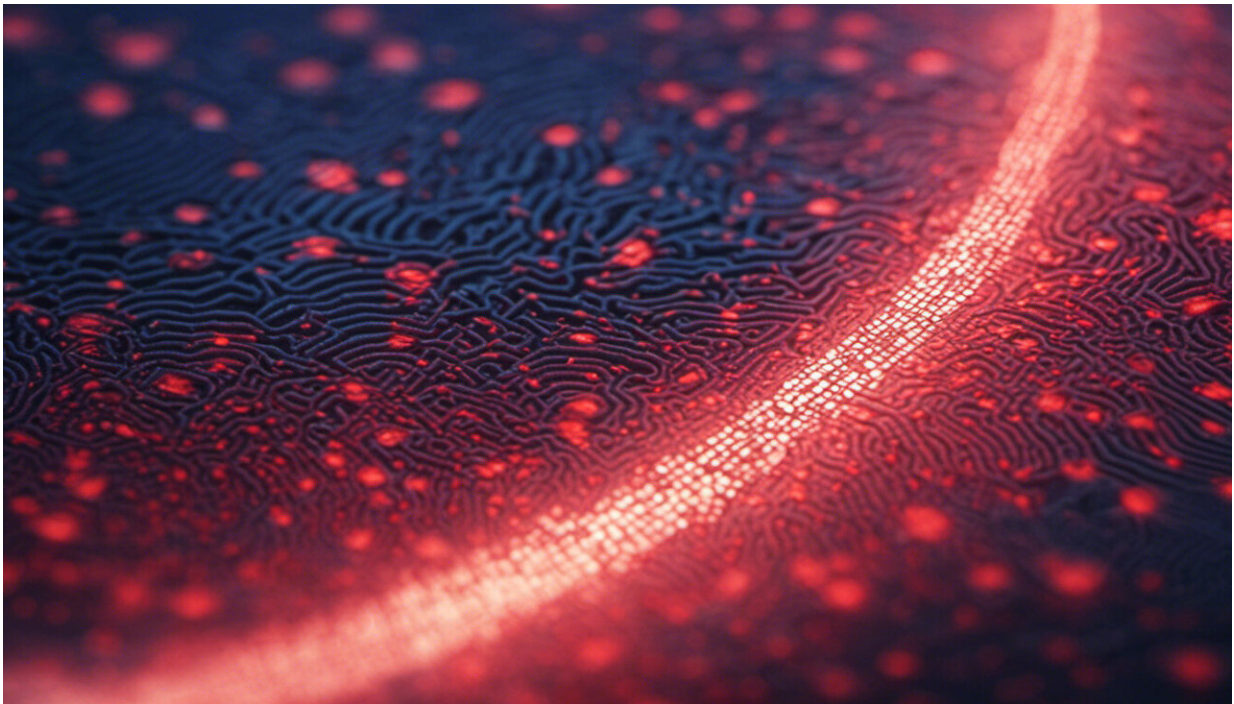


Could we safely reduce the frequency of treatments for HIV-positive people?

December 1 2017, by Caroline Petit



Credit: AI-generated image ([disclaimer](#))

Most HIV-positive people in France under treatment take a daily dose of antiviral drugs for life. However, a major trial is currently underway that may confirm that patients could omit several days of treatment a week without risk to their health.

In France, some 300 [patients](#) have already switched to a [treatment](#) mode called "Intermittent in short cycles," taking their medication four days a week instead of the seven currently required. The small protocol began several years ago and the patients are doing well.

In September 2017, the French Agency for Research on HIV/AIDS, [ANRS](#), launched a large clinical trial called Quatuor (Quartet in English). [Its aim is to show:](#)

"the non-inferiority of antiretroviral treatment taken 4 consecutive days a week versus continuous therapy – the current protocol – in HIV-infected patients with controlled [viral load](#) for at least 12 months and stable antiretroviral treatment since 4 months."

The trial involves 640 volunteers recruited from 63 public hospitals in France and the Caribbean. [Dr. Pierre de Truchis](#), at Raymond Poincaré Hospital in Garches (Hauts-de-Seine), is the principal investigator.

While the trial is still underway, doctors may well suggest that some of their patients living with HIV switch to only four treatments per week. Indeed, such a possibility was confirmed in May 2017 by the [National Council for AIDS and Hepatitis](#) (CNS), even as the organisations remained cautious:

"On a case-by-case basis, in conditions similar to those of carried-out studies, a discontinuous-take strategy, 4 or 5 days out of 7, may be considered."

It should be emphasized that any such change requires a rigorous medical follow-up, with close biological examinations of the patient.

Four-days-a-week treatment, in the making for 15

years

We now have 15 years of experience concerning the safety of maintenance medicine treatments alleviated with short breaks. The primary experiment has been conducted since 2003 as part of a protocol called [ICCARRE](#), acronym for "intermittent in close cycles, antiretrovirals remain effective." Led by Dr. Jacques Leibowitch of the Raymond Poincaré Hospital, a group of 48 patients went from seven to five days of treatment per week, and then to four. Despite the reduction, their viral load remained below detection level. The results were considered sufficiently robust by the international scientific community that they were published in 2010 by the [FASEB Journal](#). Similar observations on 94 patients led to a [second publication in 2015](#), adding additional years of experience.

In 2009, Assistance Publique-Hôpitaux de Paris (AP-HP) and Versailles Saint-Quentin University jointly filed for two international patents, one for "maintenance therapies under any standard triple combination" taken four days a week or less, the other for the use to that purpose of innovative quadruple combination therapies.

A first clinical trial nationwide

Convinced by the first results of the ICCARRE protocol, ANRS launched in 2014 its first clinical trial called 4-D (four days) over two years at 17 medical centres in France. More applications to participate in the trial were received than could be accepted, indicated Professor Christian Perronne, the trial's principal investigator. The results presented at the 2016 International AIDS Conference in Durban, South Africa, and [published in Journal of Antimicrobial Chemotherapy](#), indicate that [96 of the 100 patients](#) who scrupulously followed the "four consecutive days out of seven" pattern were 100% successful. Early in

the fourth week of the study three patients had a newly detectable viral load, which became undetectable upon the return to daily treatment. One patient left the study.

The results were sufficiently encouraging that the ANRS continued with the Quatuor test. To allow a comparison, it includes a "control" group consisting of patients who continue to take their treatment seven days a week for 48 weeks. This methodology meets the requirements of health authorities for the level of evidence to accumulate before a change in prescribing recommendations. According to the ANRS:

"Quartet seeks to demonstrate that the strategy four days out of seven is non-inferior to the seven days a week strategy and that at equal efficiency, patients in the relief group will get secondary benefits [fewer side effects, better compliance...]."

Negative effects of daily treatment

Experience has shown that daily treatments with anti-retroviral drugs can have substantial negative side effects. These include nausea, diarrhoea and fatigue. As a consequence, some patients take their treatment less consistently than they should – a problem that arises in many chronic diseases. Yet it is risky for patients to reduce their own treatment without medical supervision.

Reducing the treatment frequency may reduce the negative side effects of HIV drugs. A four-days-a-week regime is each year [the equivalent of five treatment-free months](#) the individual patient, a significant reduction.

What will happen from here? The full results of the Quatuor trial will be available at the earliest in 2019, at which time it may be possible in France to officially recommend the four-days-a-week treatment. Internationally, the results of the study will not necessarily be followed,

even in the United States. Yet this is the country that in 2001 first opened the path to intermittence treatments, which was then followed by Dr. Leibowitch.

It's worth asking why, more than 15 years later, the reduction of treatment still remains at the experimental level. In France, a number of HIV/AIDS associations have not yet fully grasped this issue. Instead, they have focused on preventive treatments, including as [pre-exposure prophylaxis](#) (PrEP). Under the impetus of artist Richard Cross, some of Dr. Leibowitch's patients have created an association, [The Friends of ICCARRE](#) that aims to promote the possibility of a lightened treatment program.

Doctors' freedom to prescribe as they see fit

Only a few AIDS clinicians in France have begun to lighten their patients' prescriptions. Article 8 of the [French Code of Medical Ethics](#) allows them so:

"Within lawful limits and taking into account the data acquired in science, a doctor is free to write prescriptions that he considers as most appropriate to the circumstances."

The continuing dominance of the daily treatment regime may be explained by resistance to change – which is not unique to physicians – and by the difficulty of questioning established rules within the medical community. Other factors can play a role as well, including the caution of patients and physicians, as well as doctors' fear of lawsuits.

Another factor is the influence of the pharmaceutical industry on medical authorities' choices. After all, four days of treatment rather than seven represents 42 percent reduction in drugs. If expanded throughout France, such a treatment program would in a savings of some 500

million euros for the national health system each year (based on 100,000 patients on treatment, with an average monthly cost per patient of 1,000 euros). The question of the cost has larger ethical and humanitarian implications as well, particularly at a time when 22 million HIV-positive people still do not have access to triple therapy.

An additional trial, called "big ICCARRE," also led by Dr. Leibowitch, is exploring the possibility of that HIV treatment can safely be reduced to three, two or even one day per week, while maintaining a controlled viral load in patients. This research pursues the objective of finding the medical dosage that is both necessary and sufficient for each patient, and is in accordance with the phrase often attributed to Hippocrates, "[First do no harm.](#)"

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