

Hold everything! An overview of structured interruptions to HIV therapy.



AFAO/NAPWA Education Discussion Paper. Vol. 2, No. 2, 2000/2001

Kirsty Machon

More than three years on from what US activist Eric Rofes dubbed the Protease Moment, the wears and tears of combination therapy are beginning to show. It might have been easier to “adhere” to complicated regimens, and to suffer side effects, if the scientific optimism of the protease prophets had been borne out.

The early enthusiasm for triple therapy was partly fuelled by speculation that HIV could be “eradicated” from the body through drug combinations containing protease inhibitors. Initially, it was estimated that this process would take about three years. This figure, rather like a tax, has been creeping up steadily ever since. The latest research suggests it might take anything up to 63 years before ‘latent’ cells infected with HIV and resting in the body’s lymph nodes actually decay and die. So even if antiviral drugs could wipe out all the HIV in the bloodstream, there would still be replication-competent virus in lymph nodes and other “reservoirs”, which would be capable of eventually causing damage to the immune system if the cells should ever become activated. And this virus is now thought to hang around for a long time: much longer than the amount of time most people would care to be on antiviral treatments.

So should we be surprised, then, that one of the most pressing of the emerging issues facing people living with HIV relates to the question of whether or not and under what conditions it might be safe to stop taking HIV antivirals — even for short periods of time. That there be some public debate about this has now become a matter of urgency.

There is little agreement within the medical community as to whether breaks from antiviral therapy should ever be sanctioned for any reason. Many doctors, if quizzed, will refer to studies which show how quickly viral load can rise after stopping drug treatment, and hedge their bets. However, it is also the case that people are deciding for themselves (and sometimes on the basis of limited or even incorrect information) to stop taking their drugs — and in some cases, not telling their doctors about this for fear of repercussions. In other cases, doctors are indeed monitoring and managing people through treatment breaks, for a variety of reasons. As some doctors point out, we do know that poor adherence to drugs is a major factor in sub-optimal response to

therapy, or so-called “treatment failure”, and if a patient is not in a position to manage a complicated therapeutic regimen, it may be that they are indeed, better off taking a break, and taking the time to re-assess their preparedness for treatment.

Terminology

The term “drug holiday” now has a widespread currency among PLWHA and doctors, but it is in fact, quite misleading. The term was initially coined to describe the not-uncommon practice of stopping treatments for short periods, in order to better enjoy special events like Mardi Gras weekends or camping trips. However, it has now become a “catch-all” term used to describe breaks from therapy in general: whether these breaks occur in a ‘structured’ way (after discussion with a doctor), or a person simply decides to “go off their drugs” for a day, a week, “a while”. Structured interruptions to ongoing treatment are more accurately referred to as “pulse therapy”.

“Strategic interruptions to therapy” are likely to become the preferred term.

Treatment breaks in early infection

It is important at this point to make a distinction, before going on to look at the evidence for and against different kinds of treatment breaks. Most of the limited research about treatment breaks has involved people who started taking antiviral drugs at seroconversion, or during primary infection. However, these people are in a very different immunological position compared to people who began treatments at a later stage in HIV infection. It is thought that people treated during primary infection, and who have managed to keep virus suppressed at consistently undetectable levels, have maintained the potential for some of the key immune responses to HIV.

As with other viruses and infections, the body does mount an initial immune response to HIV. This includes the production of antibodies, and of cells which specifically seek and kill other cells if they are infected with HIV. If antiviral treatment is able to drive viral load down and maintain this at extremely low or undetectable levels, these immune responses to HIV will not occur, because there will not be enough HIV protein around for the immune cells to

respond to.

However, in many people who treat HIV very early, the virus has not had the opportunity to cause any of the damage to the immune system found in later stages of infection. So some researchers believe that the body will maintain certain important elements of an immune response to HIV. The theory behind structured interruptions to therapy in people treated early is this: if therapy is stopped for a short period, the virus will begin to replicate, and the immune system, recognising the virus, will respond, and mount an attack against HIV-infected cells. If viral load begins to rise again, antiviral therapy will then be used to suppress virus again.

Over a long period of time, the immune system may become so effective at fighting HIV on its own that the need for antiviral drug suppression becomes less and less. However, while research continues, there is not nearly enough evidence to 'prove' that preserving these immune cells will *necessarily* lead to long-term suppression of HIV in the absence of antiviral treatment.

'Evidence' for this approach

It seems there is some flimsy evidence to support this theory, some of it presented at the Chicago retroviruses conference earlier this year. Dr Marty Markowitz, from the Aaron Diamond AIDS Research Centre in New York, reported on a small study of people who had discontinued treatment after an average of about 18 months on treatment.

There are two critical caveats to this study. Firstly, it was very small (just four people), and secondly, all four people had been treated very early, and all had undetectable virus (below 400 copies). When therapy was stopped, two of them were able to maintain virus below 400 copies after stopping therapy: one for 14 months, and one for 21 months. However, the other two saw their virus rise back to baseline (pre-treatment) levels. This study is at best suggestive, and it would be impossible to draw any meaningful conclusion from the experience of the two patients who stayed undetectable for 14 and 21 months.

A second study from Chicago was presented by Dr Franco Lori, who looked at the case of three people taking AZT, 3TC and zidovudine. All had high viral loads (between 16,000 and 720,000 copies), and started treatment within one year of infection. They were put on a 'structured' series of breaks from therapy. Three weeks of treatment was followed by a complete break (or interruption), which continued until viral load rose to 5,000 copies. The patients then began treating again (with the same combination). After three months, treatment stopped again. The researchers noted that following each successive interruption to treatment, the time in which it took for viral load to rebound to 5,000 increased: from one week after the first break to an average of 37 days third time round.

As with the Markowitz study, this is far from

"evidence" that structured interruptions to treatment, or pulse therapy, have a role in managing HIV. It is Dr Lori's view this approach may only be applicable in people who actually start treatment in the window period before seroconversion has actually occurred. He was moved to warn that the data was experimental, and should not be used to justify changes to current treatment strategies.

The 'Berlin patient' hype

Most discussions about stopping therapy are likely to touch on the so-called Berlin patient. The case of this one man has garnered an enormous amount of attention worldwide, and has been frequently held up as exemplifying the argument that early treatment of HIV can lead to eradication, or at least to ongoing successful viral suppression without therapy.

The 'Berlin patient' was treated close to the time of his seroconversion with a combination of hydroxyurea, indinavir and ddI. At the time he commenced therapy, he had a high viral load (90,000) but was antibody negative. The triple combination therapy was immediately effective in suppressing his viral load to below 500 copies (undetectable). After a few months, the man stopped his anti-HIV medications due to an infection (for which he took antibiotics), and, as might be expected, his viral load increased. He re-started the same combination of drugs, and then stopped again after experiencing another infection. This time, however, his viral load did not rise. It remained well below the level of detection, and only through the most high-tech analyses of his lymph nodes have doctors yielded any evidence of HIV whatsoever in this man's body.

More recent reports indicate the Berlin patient also maintains one of the critical immune responses against HIV: the production of immune cells called cytotoxic T-lymphocytes, which can kill cells infected with HIV.

The significance of this one patient remains unclear, and it is not clear that we should expect such results to ever be widely duplicated. What's abundantly clear is that the situation of the Berlin patient, whose case is most unusual, should not be taken to mean that stopping therapy is generally safe, or even beneficial. But frustratingly, the Berlin patient's case has been widely claimed as evidence in support of both treatment breaks, and of the benefits of hydroxyurea (an anti-cancer drug sometimes used to treat HIV).

Reality bites: what if a person wants to stop?

The reality is, most people taking, or contemplating, so-called "drug holidays", are not seroconverters. Practitioners seem divided on

the question of whether breaks from therapy—for any reason—should be countenanced in people who begin treating HIV at a later stage of infection. Many doctors insist (at least publicly) that any breaks from treatment at all are dangerous: an open invitation for the virus to repopulate and cause havoc (and perhaps develop drug resistance at the same time). Nonetheless, this is changing slowly, and many doctors who see lots of people with HIV have a reasonable amount of experience in managing people who have come off therapy.

HIV is certainly capable of replicating very quickly, and the principles of combination antiviral treatment are based on a philosophy of getting viral levels as low as possible, and keeping them there. If viral load remains extremely low, so too does the level of damage to the immune system. Generally (though perplexingly, not in 100 percent of cases), if viral load is very low or undetectable, CD4 counts remain higher, and effective viral control can even lead to CD4 count rises: good news in terms of staving off opportunistic illness and AIDS.

The other important thing about keeping the virus at really low levels is that it dramatically decreases the likelihood of a person developing drug-resistant virus. HIV becomes drug-resistant relatively easily because it is prone to changes in its genetic makeup each time it replicates. Over a period of time, these changes may allow the virus to escape the control of certain anti-HIV drugs (or in some cases, whole groups of drugs). This resistant virus eventually starts to multiply unchecked, and so we have get the now-familiar rises in viral load and potential for immune damage associated with drug resistance.

However, if viral load is low or undetectable, and is staying at that level, it means very little, if any, viral replication is happening. If HIV is replicating at negligible levels (or not at all), then there is little opportunity for the mutations that can lead to drug resistance. One of the great concerns about interrupting treatment is that this may lead to drug resistance, and limit or drastically foreshorten ongoing treatment options. The third factor is evidence about HIV itself, which shows that after stopping therapy, viral load can rebound incredibly quickly, with the level of virus in some cases doubling every two days. It's what this means, and whether it can be as quickly suppressed on resumption of therapy, that research is set to focus on.

'I'd rather drink sump oil than take another pill'

This 'round-up' of medical evidence gathered in laboratories and the rarified world of studies and clinical trials ignores one obvious point: the reasons for which people might want to take breaks from treatments. To name but a few: lipodystrophy; facial wasting; nausea; diarrhoea; kidney stones; drug interactions; double-digit pill regimens; treatment fatigue; travel.

If a person wants to stop treatments because of intolerable side effects, it is often worth investigating whether switching to a different drug or combination with less side effects would be an appropriate first step. Some side effects (like diarrhoea) can be managed with a range of handy tricks and tips, some of which are quite simple, natural and non-invasive. This is an area in which education could usefully focus, since it necessitates an interactive relationship between doctor and patient, and a degree of frankness and honesty from both parties.

However, changing treatments is not the answer for everyone. It could well be that there is simply nothing to 'change to', and if the drugs are working, a person could be unnecessarily 'chewing up' future options. Besides, the argument to "just change your drugs" is hardly useful or comforting if the reason for wanting to stop therapy is not physical, but psychological. Maybe a person is feeling well, returning to work etc, and finding the high burden of pills and nauseous side effects a general imposition on a busy life. Or maybe it's a case of: "With all the pills you have to swallow, you might as well walk down the street rattling: I'd frankly rather drink sump oil."

Things to consider before any break

One of the critical factors overlooked in all the sermonising and lecturing about treatments breaks is this: if a person is taking their current combination erratically or irregularly (for whatever reason), this is potentially more problematic than stopping altogether for a break. The reason why it's important to take HIV therapies pretty much to the letter is that suboptimal drug levels in blood create the perfect situation for resistance to emerge.

Dr David Butcher, a well-known HIV clinician from the USA, says that when his patients report problems adhering to a particular drug regimen, and these problems cannot be resolved, he prefers to pull the patient off all treatments altogether, and work on the adherence issues. He has sometimes done this for periods of up to six months.

If a person is considering a treatment break, it may be best to stop all drugs at the same time, rather than just stopping the drug which is causing a person trouble or side effects.

Monitoring and prophylaxis

Treatments breaks are something that really need to happen in close consultation with a doctor. This is important because of the capacity for viral load to rapidly rise. It would be best to have viral load and CD4 counts checked regularly during any interruption to treatment, so that if either reaches a level at which patient or doctor feels uncomfortable, or at risk, they can re-consider or discuss whether to go back on treatments.

The role of CD4 counts needs to be stressed here, since recently, British guidelines for HIV treatments were amended, suggesting that a CD4 count as low

as 350 (not 500) could be safely reached before the risk of immune damage outweighs the potential risks of long-term therapy and/or toxicities.

For some people, however, part of the psychological importance of a treatments break is precisely about *not* seeing a doctor or undergoing any monitoring.

Though most medical practitioners would be likely horrified by this prospect, some people report that this is part of 'freeing' oneself (if only for a short time) from the tyranny of checkups, appointments, blood tests and the relentless white noise of health maintenance.

For people in this position, there are a couple of things to stress. The first is to be generally aware of one's state of health, including the potential symptoms of any opportunistic infections or illnesses, especially for people who have stopped treatments with a high viral load or low CD4 count. One of the realities of stopping treatment is that it might well put a person at risk of an OI. (In one case I know of, a person on a treatments break developed the life-threatening opportunistic disease PML). Opportunistic infections can be better managed and treated if diagnosed early. People may also want to think about starting or continuing prophylactic drugs (for example, the antibiotic Bactrim to prevent PCP). Some people may find this idea defeats the entire philosophy of a 'treatments break'. But this relatively low-maintenance intervention could prevent much more serious, debilitating and invasive medical interventions down the track.

The 'great experiment'

Many HIV-experienced GPs understand that so-called drug holidays are a fact of life in managing HIV — and one that isn't going to go away by ignoring the issue. On the basis of the medical evidence alone, drug holidays are at best a moderate risk and at worst, dangerous. The exception appears to be among people treated very early in infection, a group in whom there is more evidence than others for the effectiveness of this strategy.

There is a feeling that clinical research in this area needs to be urgently conducted, and some trials are likely to begin shortly in Australia.

However, test-tube understandings of HIV are a million miles from the daily reality of triple (or more) therapy. If a person's GP is absolutely adamant that he or she will not discuss the person's wish to stop treatment, it may be best to seek advice elsewhere. It may be one doctor doesn't endorse it, but we should be worried if they refused to entertain a discussion.

It seems clear that what is more dangerous than a well-planned and monitored break from HIV treatments is to take antiviral drugs in an erratic or sporadic manner, or to stop therapy cold without advice, support or plans for contingency.