Community recommendations for clinical research involving antiretroviral treatment interruptions

Introduction

This brief review provides community recommendations for research that requires HIV-positive people to interrupt antiretroviral treatment (ART).

We recognize that there are important scientific questions that can only be answered by stopping ART. Examples can include research to either cure HIV or to induce a long-term immune response capable of suppressing HIV in the absence of ongoing ART. Experimental approaches include immune-based therapies, therapeutic vaccines and treatments intended to reduce or clear HIV reservoirs.

This type of research is very important and it is widely supported by both the scientific and advocacy communities. However, it raises safety and informed consent issues because treatment interruptions are not generally recommended in treatment guidelines. This is largely because the Strategies for the Management of Antiretroviral Therapy (SMART) study found that stopping treatment increases the risk of serious and fatal illness compared to continuous therapy[1].

We recognise that some HIV positive people may very willing to interrupt treatment as participants in this research. However, for ethical reasons, there is a need for:

(i) The use of study designs that minimise risks to participants, including by excluding those likely to be at highest risk of adverse outcomes; and

(ii) Provision of clear information that explains both absolute and relative risks of a treatment interruption as part of the informed consent.

Summary of results from SMART

The serious negative outcomes in the SMART study were strongly associated with the increase in inflammation that accompanies viral load rebound after treatment is stopped[2,3]. Furthermore, individuals in SMART who interrupted treatment continued to face a significant increase in the risk of illness and death after restarting ART compared to people on continuous ART[4]. Although some scientists have attempted to critique the SMART findings[5], these critiques have not stood up to scrutiny[6].

Because SMART was a very large randomised study – involving 5,472 people – the results are widely considered to be robust and unequivocal. Similar results have also been reported by large observational studies[7,8,9] and a randomized trial in West Africa[10]. The importance of the association between viral load levels and health outcomes has also subsequently been reinforced by studies linking cumulative exposure to viral load and risk of morbidity and mortality (the higher the amount of unsuppressed viral load and the longer the duration of exposure, the greater the risk)[11,12 ,13].

Previous studies that reported stopping treatment as a safe option were much smaller and used different designs. Furthermore, some of these studies reported illnesses and deaths among individuals undergoing treatment interruption, from similar causes to those observed in SMART (such as heart disease), but the study investigators did not consider these outcomes to be related to the interruption[14].

In another observational study, individuals who died during a short-term (<3 month) interruption were assumed to be at the end stage of disease and not included in analyses[15].

Although a subsequent study suggested that interruptions are safer at higher CD4 counts – ART was interrupted at CD4 counts over 700 and reinitiated if they dropped to 350 – this was a much smaller trial than SMART (with only 329 participants) and the potential for long-term harm related to increased inflammation accompanying viral load rebound cannot be ruled out[16].

Text Box:

Common Treatment Interruption Trial Designs

The three most common types of treatment interruption trial designs are:

(1) Time to a specific CD4 T cell count threshold after interruption (as was the case in SMART).

(2) Fixed time period (typically 12 or 16 weeks) with the goal of measuring set-point viral load.

(3) Time to viral load rebound above the limit of detection (or other specified viral load threshold).

Health risks to participants are considered to decline with each type, with (3) being the safest.

Designing Studies to Minimize Risk

Because of the results from SMART and other studies, potential study participants will need to understand the risks associated with treatment interruptions. Investigators designing trials involving interruptions must show the steps they have taken to respond to the SMART results and minimize the potential risks.

For example, one research group investigating a therapeutic vaccine candidate published a comparative analysis of their trial design and outcomes among SMART trial participants, leading them to suggest that, in the context of their trial design, a 16-week interruption would likely be safe[17].

However, these types of comparisons are based on the assumption that illnesses and deaths that occurred after 16 weeks of ART interruption in SMART were not delayed manifestations of the inflammation that accompanies viral load rebound, and this assumption may be incorrect.

Another proposed method for minimizing risk involves restarting ART as soon as viral load becomes detectable during a treatment interruption. According to results presented at a scientific conference in 2012[18], intensive monitoring (three times a week) during an interruption was able to greatly limit the magnitude of viral load rebound and prevent any decline in CD4 T cell count.

This type of study design is likely to represent the safest possible approach to conducting treatment interruptions for research purposes. The lack of impact on CD4 T cell count also suggests that lower CD4 T cell thresholds could be considered when establishing entry criteria for this specific type of treatment interruption protocol. However, the design may not be appropriate for all therapeutic interventions; for example some gene therapy trials are requiring a longer period of viral load rebound because of evidence this may favour the survival and expansion of gene-modified cells.

In an effort to reduce the need for treatment interruption trials, a large research study is being planned which aims to identify biological markers that predict control of HIV viral load after ART is stopped. If successful, this will allow early studies of new approaches to measure the biomarker instead of needing to conduct ART interruptions (March 24, 2014 email from SG Deeks).

Current Recommendations

Treatment guidelines now only recommend interrupting treatment if there is a clear clinical need, such as another serious health complication. Research that involves interruptions in treatment therefore involves an intervention that is against the current standard-of-care. These special circumstances require that HIV positive people who enrol in this research understand the risks and benefits involved.

The following recommendations are included as a guide for patient material included in informed consent sheets.

Potential trial participants need to be informed that:

1. **Interrupting treatment is not recommended in clinical guidelines.**

2. **A treatment interruption may increase their risk of a serious complication, including death.**

3. **For some people the absolute risk from a single short interruption is likely to be low, and the magnitude of this risk is influenced by the following factors:**

   i) **The CD4 count when interrupting treatment.**
   The higher the CD4 count when interrupting treatment, the lower the absolute risk of a complication.

Recommendation: For study designs involving extended interruptions, CD4 counts should be higher than 700 when interrupting treatment. For study designs involving frequent monitoring that restart ART as soon as viral load becomes detectable, CD4 counts should be higher than 350 when interrupting treatment.

ii) **The lowest ever CD4 count (CD4 nadir).**
The lower someone's CD4 nadir, the higher the risk from interrupting treatment. This is related to a faster CD4 drop when treatment is stopped and a reduced likelihood of their CD4 count recovering when they restart treatment. In the SMART study, 18 months after restarting treatment, CD4 counts remained on average 150 cell/mm3 lower than when treatment was interrupted[4]. This is also likely to be related to the duration of the interruption.

Recommendation: Ideally, a CD4 nadir higher than 350 should be considered as entry criteria for studies considering interrupting treatment. This criterion may be more flexible for study designs involving frequent monitoring that restart ART as soon as viral load becomes detectable.

iii) **Background health: cardiovascular risk.**
Given that cardiovascular disease (CVD) was one of the most common complications seen in people interrupting treatment in the SMART study, baseline cardiovascular evaluation should reduce the chance that patients at higher risk of a heart attack are enrolled into studies. The inflammation caused by discontinuing treatment is likely to be a risk factor for heart disease.

Recommendation: EKG and stress tests should be included in trial screening to rule out subclinical CVD, along with a fasting lipid panel and CRP levels. A history of cardiovascular disease or a >10% 10-year Framingham risk score should be exclusion criteria for trials involving treatment interruption. Recreational use of stimulants with the potential to increase risk of a heart attack, such as cocaine and methamphetamine, should also be exclusion criteria.

iv) **Background health: liver disease.**
Based on the results from SMART, people with hepatitis B or C face a higher risk from complications from stopping treatment[19].

Recommendation: People with HIV and hepatitis B or C coinfection should not be enrolled in treatment interruption studies. The safety of treatment interruptions in people with a history of hepatitis B or C that has been cured is not known, and it may be appropriate to also exclude individuals with a prior history of hepatitis coinfection.

v) **Background health: other comorbidities.**

Detectable viral load has been shown to impair control of comorbidities such as diabetes and hypertension[20].

Recommendation: The presence of comorbidities such as diabetes, hypertension and kidney disease should be exclusion criteria for treatment interruption studies.

vi) **Age:** Older individuals had a significantly increased risk of mortality in SMART.

Recommendation: Individuals over 55 years of age should be excluded from (or strongly cautioned against) treatment interruption trials. This criterion may be more flexible for study designs involving frequent monitoring that restart ART as soon as viral load becomes detectable.

vii) **Smoking:** smoking was also significantly associated with mortality in SMART, and should perhaps be included in the exclusion criteria, although the evidence for this is less strong as the key is the overall CV risk.

viii) **The level of viral rebound when off treatment**
Although the SMART investigators are still analysing their results to see whether they can identify which patients are at highest risk from a treatment interruption, their early results have shown some important predictors.

Risks were related not just to CD4 count, but to how quickly viral load rebounded. They also found that higher baseline levels of some inflammatory biomarkers correlated with the highest risk.

Although d-Dimer and IL-6 results from SMART are still preliminary, this research should be followed with a view to validating these inflammatory biomarkers as additional screening tools to enhance safety.

Recommendation: Participants should be closely monitored (at least every 2 weeks) for viral load rebound and patients rebounding to >50,000 copies/mL should be recommended to restart treatment. Whenever possible (e.g. in studies of interventions where the aim is to maintain undetectable viral load after ART is stopped) treatment interruption study designs should call for restarting treatment as soon as viral load is confirmed to have rebounded to detectable levels.

viii) **The CD4 count level used to restart treatment in the study.**
Restarting treatment at higher CD4 counts will minimise the risk of new infections. Letting CD4 counts fall even to 250 may increase the risk of health complications.

Recommendation: Research that involves patient interrupting treatment should restart treatment before their CD4 count falls below 500. This brings use of treatment within current US guideline recommendations.

ix) **The duration of the treatment interruption.**
The shorter the interruption, the safer it is likely to be. In SMART the differences in the risk of illness and death between patients on continuous treatment or taking an interruption became apparent four months after stopping ART and became more significant after six months. Although this finding has been interpreted as offering some reassurance regarding the dangers of short ART interruptions, it must be stressed that it remains possible that the increased risk of illness and death documented in SMART represented a delayed effect of inflammatory events that occurred earlier during the ART interruption.

Recommendation: Based on the SMART results, a treatment interruption in a research study should be no longer than four months maximum, preferably less. As noted above, whenever possible treatment interruption study designs should call for restarting treatment as soon as viral load is confirmed to have rebounded to detectable levels. There may be exceptions in cases where there is compelling evidence that a specific therapeutic intervention (such as a gene therapy) may produce a slower decline of viral load to undetectable levels..

4. **If viral load rebound occurs during a treatment interruption, the risk of transmitting HIV is increased.**

5. **Special consideration is required when interrupting antiretroviral regimens containing drugs with long half-lives:** Because non-nucleoside reverse transcriptase inhibitors (NNRTIs) and some nucleoside/nucleotide reverse transcriptase inhibitors (emtricitabine and tenofovir) stay in the body longer than other antiretroviral drugs after stopping, there is a risk of HIV developing resistance mutations[21]. A variety of strategies have been proposed to address this problem (described in a freely accessible review by David Back and colleagues from 2007[22]), including switching drugs prior to interruption, or using lopinavir/ritonavir for a month after the combination antiretroviral regimen is stopped. An initial study of the latter approach has suggested that it can be effective[23].

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The recommendations are suggested as good practice for future research and to inform HIV-positive people interested in supporting this research as study participants.

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