

Emergency guidance on ART forced treatment interruptions due to drug unavailability (forced stock-outs) for people living with HIV and their care providers in Europe and Central Asia

Issued by the European AIDS Treatment Group, October 2011

Introduction

This guidance, issued by the European AIDS Treatment Group (EATG), seeks to inform and provide assistance to people living with HIV and their care-takers in case of an antiretroviral (ARV) treatment interruption.

It is released in an emergency situation, at a time when HIV advocates and UN agencies register ARV treatment interruptions due to stock-outs in several countries within Europe and Central Asia. The EATG works on removing and preventing treatment interruptions and calls on national authorities, along with technical support providers and donors, to improve

- Forecast and timely and sufficient funding allocation,
- Efficacy of resources first of all, and facilitate price negotiations
- Procurement and supply management of ARV and other medicines.

Whereas European and WHO Europe clinical guidelines for HIV treatment exist, currently no clinical guidance for this emergency situation is available. In the absence of clinical guidelines, we seek to inform individual HIV patients about the nature and effect of treatment interruptions from an expert patient point of view, and to provide advice to individual patients on what they could do to reduce harm resulting from any interruptions.

This by no means implies that we accept the non-implementation of EACS or WHO Europe clinical guidelines: ARV treatment interruptions cause harm to the individual patient and to public health, increases the costs of treatment, and constitute a violation of the human rights of people living with HIV. The International Covenant on Economic, Social and Cultural Rights, adopted in 1966 recognises "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health".

No responsibility for any harm which may result from this guidance can be taken.

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1. What does treatment interruption mean?

A treatment interruption is when you stop taking your antiretroviral drugs for any reason. After the interruption of your treatment the drugs you take will leave your body, the replication of HIV will restart and plasma viral load will return towards the level before treatment initiation.¹

2. What happens to your health in case of a treatment interruption?

When you stop your treatment, the increasing viral load will lower your CD4 count. This may occur within weeks to a few months, in particular if the CD4 count before you ever started treatment was low. This means that, within a relatively short time, the risk that your CD4 count will return to the level before treatment initiation is high¹.

This process may be accompanied by clinical symptoms such as tiredness, depression, sometimes fever and swollen lymph nodes, soreness and sometimes opportunistic infections as well (similar to signs and symptoms observed soon after becoming infected with HIV).²

3. Who is at particular risk in case of a treatment interruption?

Treatment interruption is always risky, but it may be particularly dangerous for those who in the past started ART at an advanced stage of their infection (CD4 count less than 200). The lower your nadir³ before treatment initiation, the higher the risk of complications.⁴

Another risk is the occurrence of drug associated resistance (discussed below)

4. What types of treatment interruption are there?

a. *Structured treatment interruption.*

Planned and controlled interruption of your treatment for any personal or medical reason (drug trial) that is implemented with your doctor's knowledge.

Structured treatment interruptions have been investigated by clinical trials. They are generally considered unsafe and are not recommended anymore.⁵

¹ El-Sadr, W & Neaton, J (2006) 'Episodic CD4-guided use of ART is inferior to continuous therapy: results of the SMART study'. CROI 2006 Abstract #106LB

² Kaufmann, G.R et al (2011) '[Interruptions of cART limits CD4 T-cell recovery and increases the risk for opportunistic complications and death](#)', AIDS 2011, 25:000-000

³ Also called nadir = lowest CD4 count ever measured, usually taken at treatment initiation

⁴ Kaufmann GR, Furrer H, Ledergerber B, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. Clin Infect Dis 2005;41:361-72

⁵ EACS HIV Guidelines (2011). Available at <http://www.europeanaidscinicalsociety.org/images/stories/EACS->

[Pdf/1_treatment_of_hiv_infected_adults.pdf](#) Page 19 Accessed September 2011

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b. *Drug holiday.*

You interrupt your treatment for a certain period you decide without your doctor's knowledge and control. This may carry significant risk and may lead to drug resistance. This, in turn, may render ineffective the formerly efficient drug combination you took. Thus, drug holidays are risky and unsafe, in particular in patients who started therapy at advanced HIV disease stage.⁶

c. *Treatment interruption due to stock-outs.*

Interruption of drug supply can force you to interrupt your treatment. You or your doctor may have no control over this. You may be confronted with a complete or a partial interruption (only one, or two or the entire combination therapy being concerned).

The following is advice for this last type of treatment interruption.

5. What happens if you stop treatment?

Depending on the drugs in your antiretroviral treatment, the different drugs will leave your body at different times; this relates to the so-called plasma half-life of the given drug. This indicates how fast the drug is eliminated from your body. Most antiretroviral drugs are metabolised within 24 hours. Exceptions are the following drugs – so called “long half-life drugs”:

- nucleoside analogs (NRTI) : lamivudine (Epivir, 3TC, Combivir, Trizivir and Kivexa partly, lamivir), emtricitabine, tenofovir (Viread, partly Truvada and Atripla),
- non-nucleoside analogs (NNRTI): efavirenz (Stocrin, Sustiva, Atripla partly), nevirapine (Viramune), etravirine.

The drug staying longest in your blood is efavirenz. If your combination contains any of these drugs with a longer half-life, these will remain in your body for a few days or even weeks while other drugs in the combination may have already been eliminated from your body. In such a situation your HIV may become exposed to a single drug and resistance to this drug can occur. Resistance to efavirenz and nevirapine unfolds quickly, which means you need to be protected from single exposure to either of these drugs.

If you develop drug resistance, the combination you took before the interruption may no longer be effective for you and you will have to change treatment when you re-start therapy.

In addition to the risk of developing resistance, damage may also be caused by inflammation due to viral replication.

6. How can you prevent drug resistance in this situation?

We suggest that you continue taking the short half-life drugs or a protease inhibitor for seven to fourteen days after you have stopped taking the long half-life drugs. This can protect the longer half-life drugs from being left alone in the body.

⁶ <http://www.aidsmap.com/Risks-when-stopping-NNRTIs/page/1729926/>

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A reasonable strategy, although no specific studies have been addressed to this issue, could be:

- Protease inhibitor-based regimens, raltegravir and maraviroc can all be stopped without concern;

With nevirapine and efavirenz based regimens, there are two options:

1. Stop everything and take a protease inhibitor for 14-21 days;
2. Stop nevirapine or efavirenz and take 2 nucleoside analogs (NRTI) for 7 days⁵

7. What should you do if your usual combination is not completely provided, but only some drugs are available?

This needs to be discussed in detail with your doctor in all cases. With the exception of a boosted protease inhibitor, **do not accept the offer of a single drug (one active ingredient) as an alternative**. Temporarily, in an emergency situation, a drug combination containing **two active ingredients** can be accepted especially if you are at risk because of the weakness of your immune system. However, **using a boosted protease inhibitor would be the better option** in this situation.

A treatment interruption of up to one week will not cause harm. Repeated short interruptions however are risky and will lead to resistance. If treatment supply can be restored rapidly (within one week), the same combination of drugs can be taken. However, serially repeated short interruptions (on-off-therapy) are detrimental to treatment and should be avoided by all means.

8. What happens if there is only a different drug available?

If your treatment is effective, the replacement of one or the other component with a different, effective drug can be safely done. These cases **MUST** be discussed with your doctor in detail.

9. Monitoring

CD4-counts should be monitored quarterly during a treatment interruption. With low CD4-counts e.g. antibiotics and antifungal medication may be used to prevent clinical manifestations of AIDS.

10. Advocacy guidance: stopping and preventing stockouts

- Contact national treatment advocacy groups to join their advocacy efforts.
- Reach out to doctors and medical associations to discuss the situation and possible joint action.
- You might decide to defend your rights to uninterrupted treatment in court, work on procurement and supply monitoring, do community monitoring of interruptions and publicise the problem and find solutions; particularly if the government denies that there are stock-outs.

⁵ <http://www.aidsmap.com/Risks-when-stopping-NNRTIs/page/1729926/>

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- Additionally, EATG and some groups do facilitate finding limited donations when interruptions are present.
- Some countries, notably Russia, have a community network of exchanging ARVs if doctors change their schemes.
- Also, consider contacting pharmaceutical industry representatives for emergency donations.
- Consider reaching out to international media in order to build up pressure.



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