THE USE OF LONG-ACTING ANTIVIRALS IN HIV TREATMENT

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Brief message

Hi! I am Thomas Nieuwenstein, a second-year Master's student Biomedical Sciences. I am really interested in the mechanisms of action of medication and the opportunities that novel compounds or novel regimens offer. I discovered the topic of my brief message during my internship at the Pharmacy department at the Radboud Institute of Health Science. The use of long-acting antivirals is a big topic in the department, and while my internship was not connected to this subject, the possibilities of this treatment option intrigued me and sparked my interest to write the brief message about the long-acting antiviral treatment against HIV.

Human Immunodeficiency Virus (HIV) treatment has come a long way since the introduction of the first anti-HIV treatment –azidothymidine, or better known as zidovudine, a nucleoside reverse transcriptase inhibitor– in 1987 [1]. While the drug proved to be effective at reducing opportunistic infections and AIDS-related deaths, it caused severe adverse effects in the patient population [1]. Since then, new drugs have been developed which have turned HIV into a chronic affliction rather than a death sentence [1]. Depending on which regimen is followed, the current treatment consists of one or more pills per day. Adherence to the dosing regimen is key in HIV treatment, as the virus may develop resistance to the medication in non-virologically suppressed individuals [1]. Long-acting antiretroviral drugs may offer a solution by eliminating the need for daily oral therapy [1,2].

In January 2021, the European Medicines Agency approved the first combination of sustained-release injections of non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine and integrase inhibitor (INI) cabotegravir for marketing [3]. Rilpivirine inhibits the HIV's reverse transcriptase enzyme, preventing the HIV RNA from being converted into DNA. Cabotegravir inhibits the integrase enzyme, preventing HIV DNA from being integrated into the human DNA. So far, this treatment can only be used in patients who are already virologically suppressed (<50 copies of HIV-1 RNA per mL blood) and have not developed any resistance against NNRTIs or INIs. After a four-week oral lead-in period, the injections must be given intramuscularly into the gluteus muscle once every four weeks or once every other month, depending on the dosing schedule. If a dose cannot be administered at the designated interval, the extra time can still be bridged with oral therapy. Long-acting injectable therapy of rilpivirine and cabotegravir is indicated as non-inferior to daily oral therapy of the same drugs [4]. The use of the long-acting injectables greatly reduces the medicinal burden compared to the usual daily oral therapy.

Sadly, non-adherence or dropping out of a long-acting injectable regimen is a much larger problem than in oral therapy. As the injections have a sustained release mechanism, concentrations of cabotegravir and rilpivirine can still be measured in the blood up to a year later. As these concentrations are too low to provide virological suppression, there is a high chance that the virus will develop resistance to cabotegravir or rilpivirine if viral suppression is not achieved through other means, such as oral therapy. This means

that the patients will not be able to use these long-acting injectables anymore. This may extend to other drugs in the NNRTI or INI drug class. Patients who cannot or will not continue the long-acting injectable treatment schedule should start on other (oral) treatment as soon as possible to minimise the risk of developing resistance.

The long-acting injectables have another downside, as the injectables also have more side effects, such as pain at the injection site due to the thick needle or other local reactions, on top of the drug-related side effects shared with their oral counterparts [4].

Apart from the clinical treatment of HIV, long-acting injectables have

shown to be beneficial as pre-exposure prophylaxis (PrEP) for at-risk populations, such as healthcare workers, men who have sex with men, or sex workers, to prevent infection with HIV in the first place [5]. Oral PrEP is already available but is not used often by those who could benefit most from it due to the burden of daily oral treatment. The use of monthly, or once every two months injections may be more acceptable to the populations that may benefit from PrEP and lead to a higher efficacy of PrEP treatments [5].

Overall, the long-acting injectables offer advantages over daily oral therapy but are only approved for a limited population thus far. The population for whom these long-acting injectables are currently approved are already the least vulnerable HIV-infected population (must be virologically suppressed and have good adherence to oral therapy). Exploring the options long-acting injectables could offer in more vulnerable populations, such as those that frequently forget their oral therapy, could have an even larger impact. Possible new solutions also cover other combinations of HIV drugs or non- or less invasive methods of drug delivery, such as skin patches. Research concerning expanding the population and expanding the arsenal of injectable agents is the next step in HIV treatment.

References

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2. Margolis, D.A. & Boffito, M. Long-acting antiviral agents for HIV treatment. *Curr Opin HIV AIDS* **10**, 246-252 (2015).
3. Balfour, H. First long-acting HIV treatment approved in Europe. (2021).
4. Swindells, S.*, et al.* Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. *N Engl J Med* **382**, 1112-1123 (2020).
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EXAM QUESTION

Question 7

Do you want to test your knowledge regarding immunology? Then, have a look at the exam question below.

The human immunodeficiency virus (HIV) is an example of an acquired immunodeficiency. The HIV virus infects CD4+ T-cells, leading to...

A. a reduced activation of macrophages.
B. a decreased production of anti-HIV antibodies.
C. both a reduced activation of macrophages and a decreased production of anti-HIV antibodies.

The answer to this question can be found on page 33 in this journal.