Long-acting therapies—safety and other issues to consider

Potent combination anti-HIV therapy (commonly called ART) can help control HIV disease and help some people have near-normal lifespans. However, current formulations of ART need to be taken every day, sometimes twice daily, for the rest of a person’s life.

Long-acting formulations of ART are under development. Such formulations could be offered as part of pre-exposure prophylaxis (PrEP) programs to help reduce a person’s risk for becoming HIV infected. They could also be an attractive option for some HIV-positive people who are considering treatment for the first time.

Long-acting regimens simplify dosing because they would need to be taken infrequently—perhaps every six to eight weeks. Those currently in development need to be injected into the buttocks.

According to psychologists in New York, long-acting formulations “might be a particularly good fit for patients with disclosure concerns, who would benefit from having a shot administered in the privacy of a doctor’s office, without needing to store medication on their person or in their house.”

More than five years ago, the pharmaceutical company ViiV Healthcare began to develop the experimental integrase inhibitor cabotegravir. In collaboration with another drug company called Janssen, ViiV has also been developing a long-acting formulation of rilpivirine, which belongs to a class of drugs called non-nukes.

Long-acting anti-HIV drugs have been in development longer than their oral, immediate-release counterparts. Some of the reasons for the longer development of these drugs arise because these formulations are new and have not been previously been tested in people. Below are some issues that need to be considered and explored with these experimental formulations; there are likely more.

Drug levels and safety issues

1. Long-acting formulations are slowly released from the buttocks into circulation. In order to be sure that the amount of these drugs in the blood is at least adequate to reduce production of HIV, it is very likely that patients will first have to take oral (immediate-release) formulations of these drugs. How long will this period of oral medication-taking last?

2. An advantage of first taking an oral formulation of a regimen for several months is that it may allow sufficient time for doctors and nurses to detect any bothersome side effects. Key questions still under investigation are: What dose of a long-acting medicine is needed and how often will it need to be injected?

3. Should someone taking a long-acting regimen decide to discontinue receiving this formulation, how long will the long-acting formulation remain in the body? For potential PrEP users, this is critical information to help reduce the risk for developing drug-resistant HIV should long-acting formulations be approved as PrEP.

4. Another potential safety concern is drug interactions. If a person taking a long-acting formulation also takes another medicine and there is a drug interaction affecting levels of either or both drugs, this could result in the following issues:
   - increased levels of the long-acting formulation, leading to new or intensified side effects
   - decreased levels of the long-acting formulation, leading to reduced effectiveness and rising HIV levels
   - higher-than-expected levels of the other medication, resulting in side effects
   - reduced levels of the other medication, resulting in reduced effectiveness

In the case of people taking immediate-release regimens, it is relatively easy to deal with some drug interactions
—they simply stop taking the offending medicine(s) and drug levels quickly fall. However, in the case of people taking long-acting formulations with infrequent dosing schedules, since the drug(s) is being constantly released into their system, there is no way to suddenly stop taking them.

Some conditions/treatments where drug interactions with long-acting formulations are possible may include the following:

- therapies for hepatitis C virus infection
- hormonal contraceptives
- antidepressants
- antipsychotics
- treatments for addictions

5. What do doctors do if a woman taking a long-acting formulation becomes pregnant? How do these drugs affect the growth and development of the fetus?

6. For now, long-acting therapies that are being developed as potential treatments are being tested only in people who have never previously used HIV treatment. So additional clinical trials will be necessary if treatment-experienced people wish to use these formulations.

**Other issues**

Health policy planners are only just beginning to identify issues that might occur once long-acting formulations are licensed by regulatory authorities. At a minimum, basic themes that need to be explored and understood once licensure has occurred include distribution, storage and training of staff to perform intramuscular injections and maintain good clinical record keeping so that patients are recalled for injections in a timely manner. If all goes well in phase III trials, long-acting formulations are not likely to be approved in Canada until at least 2019. As regulatory approval is relatively distant, it is premature to go into much detail about issues of how these drugs will be distributed and additional steps that may be likely to facilitate their use. However, it is noteworthy that long-acting cabotegravir does not require refrigeration but long-acting rilpivirine does. This may affect the deployment of the choice of these drugs for PrEP.

—Sean R. Hosein

**REFERENCES:**

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