AVAC

Global Advocacy for HIV Prevention

Introduction to Long-Acting Injectables

The term long-acting ARV injectable refers to an antiretroviral drug that is delivered via an injection and persists in the body for an extended period of time. These drugs are being developed as treatment for people living with HIV and as pre-exposure prophylaxis (PrEP) for HIV-negative people. The goal is to develop an injectable-only regimen that would minimize adherence requirements. For both treatment and prevention, daily dosing can be a challenge. Some people might prefer a product that is discreet and requires less frequent dosing. The candidates that are furthest along are rilpivirine (also known as TMC278, brandname Edurant) and cabotegravir-LA (also known as GSK744-LA—and is an analog of the drug dolutegravir). Injectable antibodies are also being considered for PrEP.

The physical and chemical properties of ARVs like cabotegravir and rilpivirine make them good candidates for long-acting injectables. Specifically, they are potent, poorly water-soluble and have relatively small oral doses, meaning that the volume of an injected dose will not be too high.

A drug only works if it is present in sufficient quantities in the body. Each medication is processed, or metabolized, by the body in a specific way. Some drugs are processed rapidly, others more slowly. Long-acting injectables have a long half-life, which means the drug remains in the system for a long time. This is good because it allows less frequent dosing. But it can be challenging if someone wants or needs to stop using the medication, since it takes some time for it to leave the body. For long-acting injectables, it is essential to understand how the drug is processed —the pharmacokinetics and pharmacodynamics of the drugs in the body—to be sure that a given dose leads to blood levels that are safe and effective.

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What does it take to develop a long-acting injectable for HIV treatment and prevention?

TREATMENT

Could it CONTROL the virus?

The two leading long-acting injectables, cabotegravir-LA and rilpivirine, have been evaluated as a two-drug "maintenance" regimen that could be used after a person with HIV achieved an undetectable viral load with oral triple-combination ART.

What is the right DOSE?

Data from the Phase IIb LATTE-2 study showed that dosing at 4 and 8 weeks were similar in terms of tolerability but that monthly dosing had a slightly lower rate of virological non-response. Two Phase III trials, ATLAS and FLAIR, are testing monthly dosing of the two-drug injectable regimen.

Does it WORK?

A regimen that included an "induction phase" with a three-drug oral combination, followed by a "maintenence" phase of the two-drug injection regimen of cabotegravir-LA and rilpivirine led to virologic suppression in the majority of participants. Two Phase III trials, ATLAS and FLAIR, have recently initiated to gather additional data on the regimen. Research will also explore strategies for ensuring that individuals can discontinue the drugs safely: since injectables persist in the body and there can be a "tail" of diminishing drug levels in the body after the last dose. These lower levels would be insufficient to control the virus but can lead to viral resistance if individuals don't have appropriate care during the transition.

IS IT SAFE?

Is an injection safe? How is the injectable form of the drug processed by the body?

The first step for evaluating long-acting injectables is to test the injection in healthy, HIV-negative people. These short studies (weeks or months) evaluate the tolerability and side effects of the drugs. They also provide pharmacokinetic (PK) and pharmacodynamic (PD) data: how the drug is processed by the body, and how levels of the drug change in the body over time. At this stage, dose-ranging studies gather information on the safety, tolerability, PK and PD of different dosages and regimens (e.g., one shot, two shots and so on).

TESTING THE CONCEPT

Is there evidence that an injectable could work?

To evaluate long-acting injectables for treatment, the next step is testing the oral formulations of drugs in HIV-positive people to be sure that they control viral load alone and/or in combination with other medications. Such evaluations "prove the concept" that injectable formulations could also achieve virologic control. For prevention, the concept can be tested in animal-challenge experiments, in which monkeys receive an injection and then are exposed to simian-human hybrid viruses that cause HIV-like illness.

ACCEPTABILITY

Do people want it?

A long-acting injectable for prevention and/or treatment may have potential benefits. For example, such a product might reduce adherence challenges, be used discreetly and ease some health systems challenges. But these benefits will only materialize if people want, like and use the product. Acceptability research shouldn't be an afterthought. Now is the time for product introduction planning to learn about interest in, concerns about and acceptability of the leading candidates as they are likely to be delivered.

FINDING THE RIGHT DOSE

What is the right dose and dosing schedule of an injectable?

Determining the right dose and dosing schedule for an injectable is a challenge whether the drug is going to be used for prevention or treatment. Issues related to side effects and safety are particularly pressing with a long-acting injectable since it can't be removed once it's in the body. This is one reason why people using long-acting injectables would probably start with an oral lead-in phase to establish that they could tolerate the drug.

TESTING FOR EFFICACY

EFFICACY

Does the drug work to control the virus in people living with HIV or to reduce HIV risk in HIV-negative people?

Efficacy trials of long-acting injectables for treatment are ongoing; prevention efficacy trials are ongoing and planned for 2017. In both cases, there are unique design considerations related to use of drugs that persist in the body over time, including ensuring safety at an individual level, differences due to gender, age and other factors that might impact drug metabolism and developing strategies for safe discontinuation.

PREVENTION

Could it PREVENT infection?

Cabotegravir-LA has been evaluated in a monkey model where a single monthly shot provided complete protection against repeated challenges with a simian-human virus similar to HIV. Rilpivirine hasn't been tested in monkey challenge experiments.

What is the right DOSE?

Different doses of cabotegravir-LA and rilpivirine injections have been evaluated in small trials with healthy HIV-negative men and women. These data, along with data on the drug levels associated with protection in animals, will guide selection of the dose used in efficacy trials.

Does it WORK?

Cabotegravir-LA is being tested in large efficacy trials—one that began in late-2016 and one slated to begin in 2017. It will be key to test participants regularly to detect HIV infections and minimize the risk of drug resistance. These trials will also need to explore how to provide effective treatment for people who become HIV-positive while using long-acting injectables.