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

TESTING THE CONCEPT

Is there evidence that an injectable could work?
To evaluate long-acting inyectables 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 injected. This is one reason why people using long-acting inyectables would probably start with an oral lead-in phase to establish that they could tolerate the drug.

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 inyectables 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.

Finding the Right Dose

A regimen that included an "induction phase" with a three-drug oral combination, followed by a "maintenance" phase of the two-drug injection regimen of cabotegravir-LA and rilpivirine led to virologic suppression in the majority of participants. Two Phase II 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.

Could it control the virus?
The two leading long-acting inyectables, 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.

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