



HOW HIV DRUGS GET APPROVED

WHY DOES IT TAKE SO LONG TO APPROVE NEW DRUGS?

Developing a new drug can take 10 years or more. First, drug companies must find substances that are active against HIV. Most HIV drugs are identified by testing existing drugs for anti-HIV activity (**screening**). A newer method is **rational drug design**. In this process, scientists "build" drug molecules to fight HIV in specific ways.

When a promising drug is identified, it goes through **pre-clinical testing**. This involves test-tube and animal studies. These show whether the drug works against HIV and how it works. They also show how it can be manufactured, and make sure it is not too toxic (poisonous).

If pre-clinical results are good enough, the drug company files an **Investigational New Drug (IND)** application. Then it starts testing the drug in humans (**clinical trials**). Only about 1 candidate drug in 1,000 makes it into clinical trials. When enough clinical trials are completed, the manufacturer submits an **NDA, or New Drug Application**. If the FDA approves the NDA, the drug can be sold to treat specific medical conditions.

WHAT ARE THE "PHASES" OF CLINICAL TRIALS?

There are four phases of human clinical trials. These apply to all drugs, not just drugs for HIV/AIDS. If the results from any phase of testing are not good enough, the company will stop developing the drug.

Phase I trials test the safety of new drugs for humans. These trials record the side effects that occur at different dosages of the drug. Everyone in a Phase I trial receives the new drug, but different participants may get different dosages. The trials usually study less than 100 people, and take less than a year. In Phase I trials, new drugs are given to humans for the first time. People who participate in Phase I trials face the highest risks compared to possible benefits.

Phase II trials can enroll several hundred people and take 1 to 2 years. They study how well the drug works against HIV disease. They also collect more information about side effects. Only about 1 drug candidate in 3 makes it through Phase II trials.

These trials are usually **randomized**. This means that trial participants are divided into two groups that are similar in terms of age, sex, and health. One group receives the study drug. The other group is the reference or **control** group. People in the control group get standard treatment (called "standard of care"). If there is no standard treatment, they may get a dummy medication (called a **placebo**).

Trial participants and their health care providers usually do not know who is getting the study drug or the placebo. This is called a **blinded** study. Studies are blinded so that the health care providers will be totally objective when they evaluate the health of patients in the study.

Phase III trials collect more data on a drug's effectiveness and side effects. These trials can study up to a few thousand people and often last for a year or more.

Phase III trials are normally randomized and blinded. Participants might not receive the study drug. With good results in Phase III trials, a manufacturer can apply for FDA approval to sell the new drug.

Phase IV trials are called "post-marketing studies." The regulations for Phase IV trials are not very clear, and they are not conducted very often. Phase IV trials can monitor a new drug's long-term effectiveness and side effects, or how cost-effective it is. They can also compare the new drug to other drugs approved for the same condition.

HOW DO WE KNOW IF A DRUG WORKS?

The FDA used to require trials that measured **clinical endpoints** before approving a new HIV drug. These trials analyze how many people get sicker, develop opportunistic infections, or die.

However, these trials take a long time and are very expensive. A faster, cheaper way to test new drugs is by using indirect measures of patient health. These **surrogate markers** are laboratory values such as viral load or CD4 cell counts. In 1997, the FDA approved the use of surrogate markers for full approval of new HIV drugs.

Clinical trials should include people like those who will use the drug. But manufacturers sometimes prefer to test their products in people who are as healthy as possible. For example, sometimes they exclude people infected with hepatitis B or C because of their liver problems, although many people with HIV also are infected with hepatitis.

USING UNAPPROVED DRUGS

There are three legal ways to use drugs that the FDA has not approved to treat a specific health problem:

1. **Expanded Access** is a program where manufacturers provide unapproved drugs to people who cannot take part in a clinical trial. Patients must meet conditions set by the drug manufacturer. The drugs are usually offered at no charge, but participating health care providers have to collect information on how patients respond to the drug.

2. **Treatment IND Protocol or Compassionate Use**. The FDA can allow drug companies to provide new drugs to people who are very ill and who have no other treatment options. A related type of access is called **Parallel Track**. This policy was developed to provide investigational drugs to people with AIDS who are unable to participate in clinical trials of those drugs.

3. **Off-label use**. Health care providers can write a prescription for any FDA-approved drug, even to use it for some medical condition it was not approved for. This is called **off-label use**. There may be no information about how often medications are used off-label, or how well they work. For example, interleukin-2 (see fact sheet 482) has been approved to treat cancer, so health care providers can prescribe it for people with AIDS. It has not yet been approved to treat

FOR MORE INFORMATION

The FDA Center for Drug Evaluation and Research has an informative Internet web page:

http://www.fda.gov/cder/handbook/dev_rev.htm

