

Backgrounder for FDA's HIV Patient-Focused Drug Development and HIV Cure Research Public Meeting

Introduction

On June 14, 2013, the Food and Drug Administration (FDA) will hold a public meeting to ask for comments on human immunodeficiency virus (HIV) antiviral drug development for the treatment of HIV, and HIV cure research. For the purpose of this meeting, FDA considers HIV cure research as any investigation that evaluates:

- a therapeutic intervention (or approach) that controls or eliminates HIV infection to the point that no further medical interventions are needed to maintain health; and
- preliminary scientific concepts that might ultimately lead to such a therapeutic intervention.

This meeting is part of FDA's Patient-Focused Drug Development Initiative. FDA is interested in obtaining patient input on:

- impact of HIV on daily life,
- experience with currently available therapies to treat HIV,
- patients' views on issues related to HIV cure research,
- patients' views on perceived benefits and acceptable risk for participating in HIV cure research, and
- how best to ensure clear communication of benefits and risks through informed consent.

This document is intended to provide necessary background information to facilitate meaningful discussion about current approaches to managing HIV and associated symptoms experienced by those living with HIV, and to frame important considerations to help foster a productive discussion about HIV cure research.

The meeting will be divided into two sessions. The morning session will focus on current approaches to managing HIV and on symptoms experienced because of HIV or its treatment. The afternoon session will focus on the perspectives of HIV patients and patient advocates related to HIV cure research. Each session will include brief panel discussions with an identified set of HIV patients and patient advocates, which will be followed by a facilitated audience discussion. More information about the meeting, the panels, and registration can be found at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm348598.htm>.

The **Appendix** of this document contains a discussion guide that FDA staff will use to help facilitate interaction and dialogue with participants. Questions in this discussion guide have been developed to seek insights from patients on their current approaches to managing HIV and symptoms they experience from the condition or its treatments. Additionally the guide includes questions to explore patients' perspective on HIV cure research such as their perceived benefits of participating in an HIV cure research study, what risks they might be able to accept in such studies, how they would like informed consent issues handled, and others.

Background on Patient-Focused Drug Development

The Patient-Focused Drug Development Initiative is part of FDA's performance commitments in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V). This initiative helps to provide a more systematic approach for the Agency to obtain patients' input on specific disease areas, including their perspectives on their condition, its impact on daily life, and available therapies. FDA sees Patient-Focused Drug Development as an important enhancement to our current mechanisms for getting patient input, such as Advisory Committee meetings, which are often within the context of one specific new drug application. Patients who live with a disease have a direct stake in the outcome of FDA's regulatory decisions, and are in a unique position to contribute to the understanding of their disease. FDA is committed to obtaining patient perspective on twenty disease areas during the five year course of PDUFA V. More information on Patient-Focused Drug Development is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Current HIV Treatment Options

The human immunodeficiency virus (HIV) is the virus that causes Acquired Immunodeficiency Syndrome (AIDS). During HIV infection, the virus attacks and gradually destroys the infection-fighting T-cells of the body's immune system. If the infection is not treated, the disease progresses to the final stage of HIV infection called AIDS, which is the consequence of severe damage to the immune system, leading to death.

The recommended treatment for HIV infection involves the use of anti-HIV medications, referred to as antiretroviral therapy (ART). ART prevents HIV from multiplying and destroying T- cells. This therapy requires taking a daily combination of three or more anti-HIV medications from at least two different drug classes. The drug classes include non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors, fusions inhibitors, CCR5 co-receptor antagonists, and integrase inhibitors. Although ART cannot cure HIV, it can help manage the disease and prevent progression to AIDS, help increase life expectancy in people infected with HIV, and reduce the risk of HIV transmission.

The currently approved ARTs have both short and long-term side effects which can affect daily life and adherence to the medications. The short-term effects may include diarrhea, nausea, headache, sleep disturbances and others. Other potential long-term effects of ART can range from body changes (lipoatrophy, where fat is lost from particular areas of the body, especially the arms, legs, face, and buttocks, or lipodystrophy, where fat builds up in particular parts of the body, especially the belly, breasts, and back of the neck), to kidney, liver, heart or bone effects. Suboptimal ART regimens or inconsistent adherence to ARTs can lead to drug resistance (reduction in effectiveness of current or future therapies) and progression of HIV infection (development of opportunistic infections). At this meeting, we are interested in your perspectives on how the ART side effects impact your daily life, and what HIV-associated symptoms are or are not impacted by your ART.

Why HIV Cure Research is Important

Today HIV infection is viewed as a manageable chronic infection. However, HIV is still a serious and life-threatening condition and requires life-long therapy. As mentioned above, ART can have both short-term and long-term effects. Because of these side-effects, patients are looking for ways to control or eliminate HIV infection so ART use is no longer needed.

In the past, HIV cure did not seem possible, but today, researchers are looking at new ways to either clear HIV from the body or control the virus without ART. Multiple recent anecdotal cases have demonstrated that therapeutic clearance or control of HIV infection without the need for lifelong antiretroviral therapy is at least possible, for example in patients who started ART very early after being infected, and in a case involving stem cell transplant for leukemia. These cases, although rare and isolated, have stimulated new research and resulted in renewed optimism that it may be possible to cure HIV.

The importance of HIV cure research lies in finding the right approach or combination of approaches that are both safe and effective to either clear or manage chronic HIV infection without daily ART. All HIV cure approaches being studied must be carefully balanced against the known benefits and side effects of ART. The initial interventions being tested in cure studies could have immediate and/or long-term adverse effects that could outweigh those of approved antiretroviral medications. Furthermore, and very importantly, the risks and benefits of any approach aimed at clearing or controlling HIV infection without continued treatment will need to be weighed against the risks and benefits of currently available antiretroviral therapies, including their ability to effectively control the virus and allow patients to live relatively healthy lives.

Although several possible pathways are being explored, there are significant scientific and practical challenges to develop safe and effective therapeutic approaches to cure HIV. While the initial stages of HIV cure research are essential to better understand and direct the overall scientific and drug development efforts, it is unlikely that this early research will lead directly to a cure of HIV infection for study volunteers. Instead, the information learned from early studies will pave the way for additional research. The primary goals of most early research studies are to test whether certain approaches are safe enough to continue their development, and to begin to characterize what effects they have on the virus or immune system, rather than to cure those enrolled in the studies.

Therapeutic Approaches to HIV Cure Research

Currently available antiretroviral therapies have changed HIV infection from a fatal disease to a mostly manageable chronic condition. ART can block most HIV replication but cannot clear the virus from the body. Unfortunately, this means that the virus will come back whenever a person stops taking their medication, even if they have been taking their medication for a long time. It is not completely understood how HIV maintains this viral “reservoir” to avoid being cleared during long-term ART. The virus may persist through low levels of replication that cannot be stopped by current ART, by establishing latent (hidden or dormant) infections in long-living cells, or through a combination of the two mechanisms. The ideal HIV cure would stop all ongoing HIV replication and remove all sources of HIV from the body, but no one currently knows how this can be safely and reliably done.

Progress toward an HIV cure is in very early stages of research. As described above, current HIV cure studies are designed to test the safety of certain approaches and to characterize their effects on the virus or immune system. Information learned from these early studies will help guide the next steps in development. As HIV cure research progresses, we will need to define what a successful HIV cure means, including how to detect when a patient has become cured or can safely stop taking their HIV medications. This will require more research to improve our understanding of how and where HIV survives in the body. New tests may also need to be developed to measure very low levels of virus that might remain following treatments intended to cure HIV.

Different therapeutic strategies for potential HIV cure are being explored. One approach is sometimes referred to as the “Shock and Kill” strategy. This approach aims to use drugs to “activate” virus in the reservoir and clear it from the body. This may require boosting of the immune system with other types of drugs or therapeutic vaccines to clear all of the infected cells, and will also probably require patients to remain on their ART during this entire process.

Other strategies rely on replacing or modifying the cells of the immune system with similar cells that are resistant to HIV infection. These strategies involve either transplantation of cells from donors without HIV who are naturally resistant to HIV infection, or gene therapy to modify cells collected from the patient’s own body to make them resistant to HIV infection. Some of these approaches may require use of cancer drugs (chemotherapy) to first reduce the number of the patient’s own immune cells or eliminate them altogether, in order to clear the HIV reservoir and allow the HIV-resistant cells to become established in the patient’s body. Because the use of these cancer drugs carries considerable risk to the patient, how much of the drugs are given may depend on the underlying condition of the patient. For example, HIV-infected patients with lymphoma or leukemia may receive a more aggressive treatment necessary to cure their cancer. Otherwise, HIV patients who do not have lymphoma or leukemia could receive a less aggressive approach, in order to test the research concepts.

Other research is exploring the possibility of developing a “functional” cure. Unlike the strategies discussed above, the goal of a functional cure is not necessarily to clear the viral reservoir, but to allow a person’s own immune system to control HIV without using medication. These approaches may involve the use of certain experimental drugs or therapeutic vaccines to stimulate the immune system to recognize and control active virus in the body.

Research Ethics

HIV cure research raises some challenging ethical issues, one of which is the informed consent process. At the meeting, we would like to get your input on how potential benefits and risks of HIV cure research can best be communicated clearly and accurately to prospective study participants.

The FDA reviews clinical trials designed to see if a new drug, biologic or device works (is effective) and is safe. In the setting of HIV cure research, the medical products are either drugs or biologics.

The research plan, also known as the protocol, is carefully designed to safeguard study participants and to answer specific research questions. Before a clinical trial studying a new drug or biologic can begin, the protocol must be sent to FDA and reviewed to see if it is scientifically reasonable, and safe to proceed. The protocol must also be reviewed by an institutional review board (IRB), which is a committee separate from FDA that reviews clinical trials before they can begin and while they are in progress. The IRB assures the rights and welfare of research participants are protected, and that risks from research are not unreasonable.

The informed consent process is one way of protecting research participants. Informed consent involves:

- Providing a potential participant with adequate information, including an explanation of the purpose of the research, the potential risks and benefits of the study, as well as an opportunity to ask questions to allow for an informed decision about whether or not to participate in the clinical trial
- Obtaining the potential participant’s voluntary agreement to participate, and

- Providing important information from the related ongoing research that might affect the decision to continue as a participant in the study.

Some key areas of the informed consent are:

- An explanation that the protocol involves research, and the purpose(s) of the clinical trial
- A description of what will happen during the study and identification of any experimental procedures
- A description of any foreseeable risks or discomforts
- A description of any potential benefits to the participant or to others which may reasonably be expected from the research, and
- A description of appropriate alternative procedures or courses of treatment, if any, that might be available to the participant

The purpose of HIV cure research at this early stage is to better understand and direct overall scientific and drug development efforts. It is not expected to provide direct benefit to the individual participants. It also carries risks, some of which may be unknown at this time. FDA seeks input from you as to how best to communicate this information and any other information you might want to know when deciding whether to participate in research of this kind.

Risk Assessment

The therapeutic approaches discussed above all come with known and unknown short and long-term side effects. These interventions could be more harmful than current HIV therapy with FDA-approved antiretrovirals. Multiple attempts in the past at clearing or controlling HIV infection without the need for lifelong ART were not successful, and some people were exposed to negative effects. Potential risks to patients enrolling in HIV cure research include those known and unknown risks which are unique to the drug or biologic being tested, and risks which may arise when investigational agents are combined. Many researchers acknowledge that no single intervention is likely to cure HIV and combination interventions will probably be needed. Potential long-term risks, such as serious organ toxicity or malignancy (cancer) have been identified through animal testing, but the treatment impacts in humans are not yet known. Some gene therapies, which are the use of genetically modified material to treat disease, have a known risk of malignancy or other serious side effects. There may be other risks when investigational products are combined with ART. This may include higher levels of HIV in the body because of unexpected drug interactions or other factors. In addition, some investigational interventions may require stopping or interrupting ART. This may happen at the time of the intervention because of overlapping toxicities or drug interactions, or as a test of cure after completion of the intervention. It may be difficult to quantify the potential risks associated with interrupting effective ART, but these risks include progression of HIV disease, development of drug resistance, and increased risk of HIV transmission.

Patients considering participation in HIV cure trials need to weigh the known benefits of ART against the potential and the unknown risks of any trial being conducted to advance cure as an achievable goal in HIV care. At this time, all HIV cure research is in very early stage of development. Patients need to fully understand the possible risks of any trial they are considering and the likelihood that they will not receive direct benefit from the study.

Again, the primary goal of early development is to provide evidence to support further research of promising approaches for interventions that may result in HIV cure. Future research will build step-wise on the successes and failures of these early trials.

Summary/Conclusions

The long relationship between the HIV patient community and FDA has been very fruitful, resulting in new approaches for the approval of drugs in general and for the treatment of HIV in particular. This public meeting represents a continuation of this relationship and will help advance the clinical research necessary to develop cures for HIV infection. Patients who participate in HIV cure research may, depending on the goal of the study or the nature of the product (for example: gene therapies), commit to be monitored for months to years.

It is important for the HIV patient community understands what it means to participate in a clinical study, has appropriate expectations, understand what kinds of protections exist for patients who volunteer to participate in these studies, and is fully informed in their decision to participate. To help us promote understanding, FDA is looking for input from the HIV patient community regarding your perspectives and insights on these issues, as outlined in the Appendix: Discussion Guide. The FDA considers the following important aspects of clinical research at every stage of development of a new product: the evidence showing that it works, how safe it is, what the treatment alternatives are, and the prospect of long-term safety and efficacy.

Your insight into how patients make decisions to enter into an HIV cure research study, and how best to communicate the purpose of an HIV cure research study and communicate the potential benefits and risk of participating in an HIV cure research study to patients is valuable input the FDA hopes to gain during the meeting.

Appendix: Discussion Guide

The following guide will be used at the June 14 meeting to facilitate discussion and explore patients' perspectives.

Topic 1: Patients' perspectives on current approaches to managing HIV and on symptoms experienced because of HIV or its treatment

1. What are you currently doing to help manage your HIV and any symptoms you experience because of your condition? (Examples may include prescription medicines, over-the-counter products, and other therapies including non-drug therapies such as diet modification.)
 - a. What specific symptoms do your treatments address?
 - b. How long have you been on treatment and how has your treatment regimen changed over time?
2. How well does your current treatment regimen treat any significant symptoms of your condition?
 - a. How well have these treatments worked for you as your condition has changed over time?
 - b. Are there symptoms that your current treatment regimen does not address at all, or does not treat as well as you would like?
3. What are the most significant downsides to your current treatments, and how do they affect your daily life? (Examples of downsides may include bothersome side effects, physical change to your body because of treatment, adherence to the drug regimen, going to the hospital for treatment, etc.)
4. Of all the symptoms that you experience because of your condition or because of your treatment, which 1-3 symptoms have the most significant impact on your life? (Examples may include diarrhea, insomnia, difficulty concentrating, etc.)
 - a. Are there specific activities that are important to you but that you cannot do at all or as fully as you would like because of your condition? (Examples of activities may include sleeping through the night, daily hygiene, driving, etc.)
5. Assuming there is currently no complete cure for your condition, what specific things would you look for in an ideal treatment to manage your condition?

Topic 2: Patients' perspectives on HIV Cure Research

1. What do you believe are the benefits of participating in an HIV cure research study?
2. What would motivate you to participate or to not participate in an HIV cure research study?

3. What risks would you find unacceptable for participating in an HIV cure research study, and why? (Examples of risks that may be associated with participation in an HIV cure research study include common side effects such as nausea and fatigue, and less common but serious adverse events such as blood clots, infection, seizures and cancer.)
4. In certain HIV cure research studies, you would be asked to stop any other HIV medications that you are currently taking. How would this affect your decision whether to participate in an HIV cure research study?
5. The process of informed consent is an important way for the researchers to communicate the purpose of an HIV research study, as well as its expected benefits and potential risks, so that people can make an informed decision whether to participate in the study.
 - a. How should the informed consent clearly communicate to you the purpose of an HIV cure research study, particularly when a study is designed only to provide scientific information that could guide future research and development of treatments?
 - b. How should the informed consent clearly communicate to you the potential benefits of an HIV cure research study? In particular, how can the informed consent best describe benefit when we do not know that participants in the study may gain any direct health benefits?
 - c. How should informed consent communicate clearly to you that there are potential risks of participating in an HIV cure research study, including unknown risks? In particular, how should the informed consent describe a study if there is very limited understanding about how the medications or interventions may affect participants or what the potential risks of those interventions or medications may be?
 - d. Is there any other information that you would find helpful when deciding whether to enter an HIV cure research study?
6. What else do you want FDA to know about HIV cure research from your perspective?