

The Voice of the Patient

A series of reports from the U.S. Food and Drug Administration's (FDA's)
Patient-Focused Drug Development Initiative

Human Immunodeficiency Virus (HIV)
Patient-Focused Drug Development and HIV Cure Research

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Center for Drug Evaluation and Research (CDER) and
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Introduction

On June 14, 2013, FDA held a public meeting to hear from patients infected with human immunodeficiency virus (HIV) about their perspectives on two broad areas of the disease. First, we sought to obtain patient perspectives on HIV's impact on their daily life and their views on currently available therapies. Second, we sought patient views on HIV cure research¹, with a specific focus on informed consent and ethical considerations involved in such research.

FDA conducted the meeting as part of our Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather patients' perspectives on their condition and available therapies to treat their condition. As part of this commitment, FDA is holding at least 20 public meetings over the next five years, each focused on a specific disease area. More information on this initiative can be found at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Overview of HIV treatments and HIV cure research

A background document addressing specific topics related to current HIV treatment and emerging HIV cure research, prepared by FDA specifically for this meeting, is available at <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm353829.htm>. Below are excerpts from that background document, to provide context for this meeting report.

The human immunodeficiency virus (HIV) is the virus that causes acquired immunodeficiency syndrome (AIDS). During HIV infection, the virus attacks and gradually destroys the body's infection-fighting T-cells. The recommended treatment for HIV infection involves the use of antiretroviral therapy (ART) to prevent the virus from multiplying and destroying T-cells. ART requires taking a daily combination of three or more medications. Although ART cannot cure HIV, it can help manage the viral load, thereby helping to reduce the risk of HIV transmission and prevent progression to AIDS.

ARTs have short and long-term side effects which can affect patients' daily life and in some cases, their adherence to the medications. Short-term effects include diarrhea, nausea, headache, and sleep disturbances, among others. Potential long-term effects of ART can include body changes (e.g., fat build up or depletions in particular areas of the body), kidney, liver, heart or bone side effects, and others. Suboptimal use of or inconsistent adherence to ARTs can lead to drug resistance (reduction in effectiveness of therapies) and progression of HIV infection, which can lead to AIDS and development of opportunistic infections.

Emerging research is exploring new ways to either clear HIV from the body or control the virus without ART. The primary goals of most early cure 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 on the immune system. These initial stages of HIV cure research are essential to furthering

¹ 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. It also includes any preliminary scientific concepts that might ultimately lead to such a therapeutic intervention.

overall scientific and drug development efforts. However, they are not intended, or at minimum not expected to cure HIV infection in the research study participants. Furthermore, the study drugs may pose potential short-term and long-term significant risks such as organ toxicity or cancer. Finally, some HIV cure research studies may require patients to interrupt or temporarily stop their current ART, in order to demonstrate activity of these investigational products. Participants who consider participating in HIV cure research studies must carefully weigh their reasons for wanting to participate against the often highly uncertain risks of the research study and the potential risks associated with interrupted ART.

Meeting overview

This meeting provided FDA the opportunity to hear directly from patients and patient representatives about their experiences and perspectives on HIV. Discussion focused on two key topics: 1) patients' perspectives on current approaches to managing HIV and on symptoms experienced because of HIV or its treatment, and 2) patients' perspectives on specific aspects of HIV cure research. The questions for discussion (*Appendix 1*) were published in a [Federal Register notice](#) that announced the meeting. For each topic, a panel of patients and patient representatives (*Appendix 2*) shared comments to begin the dialogue. Panel comments were followed by a facilitated discussion inviting comments from other patients and patient representatives in the audience. Participants who joined the meeting via live webcast were able to submit comments, which were periodically summarized. In-person and web participants were periodically invited to respond to polling questions (*Appendix 3*),² which provided a sense of the demographic makeup of participants, as well as how many participants shared a particular perspective on a given topic.

According to the polling questions, approximately 20 patients participated in the meeting in-person, as well as about 10 representatives from support or advocacy organizations. Approximately 10 patients or patient representations provided input through the webcast. According to polling questions conducted by FDA during the meeting, HIV patients on the panel and those who participated from the audience were generally mature adults (age 35 and older) who have lived with their condition for more than ten years, many of whom are on their third or fourth treatment regimen since being diagnosed. Although the participants at this meeting may not represent the population living with HIV as a whole, they appeared to reflect a growing demographic of HIV patients that are moving towards advanced age. It was noted by one participant that younger or minority patient populations may have been underrepresented in the in-person discussion.

To supplement the input gathered at the meeting, patients and others were encouraged to submit comments to a public [docket](#),³ which was open until July 14, 2013. Twelve comments were submitted to the docket, reflecting input from both individual patients and patient advocacy groups.

² The polling questions were intended as a discussion aid only. Polling results should not be interpreted as being representative of the overall HIV patient population.

³ A *docket* is a repository through which the public can submit electronic and written comments on specific topics to U.S. federal agencies such as FDA. More information can be found at www.regulations.gov.

More information, including the archived webcast and transcript, is available on the meeting website: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm348598.htm>.

Report overview and key themes

This report summarizes the input provided by patients and patient representatives at the meeting and through the public docket. The report is intended only to reflect the content of this meeting and is not meant to be representative in any way of the views and perceptions of any specific group of individuals or entities. Since the report reflects only the dialogue from this one meeting, there may be other aspects of HIV or its treatment not included in this report.

Several key themes emerged from the meeting:

- Much of the patient population living with HIV is aging. This brings into play many issues related to treating patients with HIV along with challenges of simultaneously treating their other chronic conditions, such as the issues of drug interactions between HIV drugs and drugs used to treat other conditions.
- The pediatric patient population living with HIV is also growing and poses very different challenges for treatment, such as the need for a different treatment approach for patients who have been on multiple therapies since childhood or birth, and therefore could have developed resistance and other medical complications relative to HIV infection.
- Patients acknowledged and greatly appreciate the advances in HIV therapy. However, these treatments still have downsides, which negatively affect patients' adherence to their treatments and their ability to manage their condition overall. These downsides include the need for daily adherence, treatment side effects, the lack of effectiveness or resistance to treatments over time, the lack of a wide range of alternative treatments, and the lingering stigma of HIV.
- Changing regimens is a critical decision for patients, many of whom are reluctant to do so because it can limit their future choices and threaten uncertainty in terms of safety and effectiveness.
- Terminology and framing is important, especially when using the terms "manageable chronic condition" and "cure research." The terms can be vague or misleading and there may be merit in exploring and testing alternative terms.
- A decision to participate in an HIV cure research trial is highly individual and personal, and likely to be widely different from one person to the next. In addition, many patients with HIV have a personal interest in participating in HIV cure research, even if it will not directly benefit them.
- Many participants believe that it is critically important to avoid any false hopes or misrepresentations of a clinical trial's intent, and to make sure patients are well informed as to whether or not a particular trial would be likely to result in benefit to the patient. They also believe that there is much room for improvement with respect to "informed consent" documents and the informed consent process.

The patient input generated through this public meeting and the docket strengthens our understanding of the current impact of HIV and its treatments. It also provides important insight into patients' perspectives on the development of future treatments for people living with HIV. FDA staff will carefully consider these perspectives as it fulfills its role in the drug development process, including when advising sponsors on their drug development programs and when assessing products under review for marketing approval. For example, *Appendix 4* shows how this input may directly support our benefit-risk assessments for products under review. This input may also be of value to the drug development process more broadly.

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

The first discussion topic focused on patients' experiences with their HIV therapies. In particular, FDA was interested in hearing about patients' perspectives on the benefits and downsides of their medications, especially their perspectives on how ART side effects impact daily life, and which HIV-associated symptoms are most significant for patients.

Four panelists provided comments to start the dialogue. The panel included three people living with HIV (one also representing an HIV patient advocacy group), and a representative from a patient advocacy organization supporting the pediatric population living with HIV. Their testimonies provided insights about what life is like for patients with HIV, ranging from an individual who was diagnosed 25 years ago and has been symptom free since, to two patients who struggle to maintain effective regimens that do not interfere with their other health issues.

Perspectives on the benefits of current treatments

Meeting participants expressed their feelings that the benefits of HIV therapy have improved dramatically over time and that for many patients, current treatments have helped transform HIV infection from a once-fatal condition to something more like a "manageable chronic condition."

One participant recognized the historic development of HIV drugs that have enabled him to have treatment that has kept him symptom-free for 25 years. Another participant shared, "there's no question medications have become more tolerable and easier to take." A participant who has been living with HIV for 26 years and who is now "undetectable,"⁴ said, "the medicines today are really doing some spectacular work in my life."

The most often cited practical benefit of current therapies was once-per-day dosing, as opposed to older treatments that required patients to remember and take their doses at multiple times throughout the course of a day. Once-per-day dosing was seen as an important contributor to improved adherence, which participants believed is critical for successful HIV management. In addition, one participant commented that a particular benefit for the newly diagnosed was a once-a-day, *single pill* regimen.

⁴ A reference to having medication reduce HIV plasma levels below the lower limit of clinical testing; however, the infection is still present, and levels will increase if medication is not continued.

Perspectives on the downsides of current treatments

Throughout the discussion, however, patients explained that many challenges and downsides remain to current HIV therapies.

- **Adherence:** The most-discussed downside to therapy was the need for strict adherence to ART, which has resulted in several challenges with therapy.
 - **Life-long therapy:** Several participants discussed non-adherence as it relates to treatments requiring a patient to remain *permanently* on therapy. One participant said that this concept becomes difficult for those who are “undetectable” and told they must still take medication, because “people don’t want to take anything if they’re feeling okay.” According to a polling question asked during the facilitated discussion, some in-person and web participants rated the burden to take medication every day as having a significant impact on their life.
 - **Side effects:** Participants commented that side effects are also a key driver of medication non-adherence. Repeated exposure to side effects was cited as a factor for non-adherence, especially for young patients.
 - **Stigma:** Participants described the role of stigma in influencing a patient’s adherence. Adherence could be affected, for example, if a person does not want family or friends to see that they take HIV medications.
- **Comorbid conditions and drug contraindications:** Another issue that was discussed by many patients was the challenge that HIV treatment poses to the management of their other health conditions. A participant described significant issues with adverse drug interactions between his HIV medications and drugs used for his other condition, high cholesterol. Another participant, also commenting on the effects of HIV treatment on comorbid conditions, said, “some of the treatments that would be the best for those conditions, I can’t have because of my antiretrovirals.” As one participant stated, it’s “the lesser of the two evils. Do I bite the bullet to continue tolerating these other conditions so that I can manage my HIV?”

One participant commented that there is a significant shortage of primary care physicians skilled in managing HIV along with other conditions. Participants reiterated that as the HIV-infected patient population ages, issues with HIV drugs and comorbid conditions will become an increasingly important aspect of the drug development landscape for HIV medications. One participant noted that many pivotal trials exclude older patients and patients with comorbid conditions.

- **Immunologic non-response:** One participant identified immunologic non-response⁵ as a downside of therapy that still exists.

⁵ In some patients, ARV therapy results in a sub-optimal increase in CD4 T-cells.

- **Improvement in viral suppression:** Another participant noted, “even though we have simpler regimens, we are not really seeing an increase in the number of people who have suppressed viral loads.”
- **Access to treatment:** One participant pointed out that people living in more populated urban areas with more sophisticated care settings have access to a wider range of treatments than those who live in more remote, rural settings. More limited access to supportive therapies such as massage therapy, herbal treatments, and acupuncture was also mentioned.

Impact of HIV and its treatment on daily life

During the discussion of Topic 1, FDA also sought to better understand the symptoms associated with HIV that are most significant to patients. As mentioned above, the term “symptoms” was used in the context of adverse effects related to either the condition or the treatment.

- **Fatigue** was mentioned as a highly significant symptom. Participants noted that fatigue was often present at different levels on any given day, and that it is often very difficult to know whether the condition or the side effects of therapy are the cause. As one participant stated, “some days I get up and I can conquer the world... and some days I just want to lay on the couch, and I never know when that’s going to be.”
- One patient who is post-menopausal said “**night sweats**” and alternating between feeling very hot and very cold were the most significant symptoms she experienced. Night sweats and “**night terrors**” were also mentioned by others.
- A few patients also mentioned concerns with **inflammation** as an inherent factor in HIV infection that can contribute to heart disease, especially as the population of people living with HIV continues to age.
- One participant stated that **peripheral neuropathy** is the side effect that most impacts his daily living. He noted, “You’re trimming your toenails and realize that you’ve cut your toe because you can’t feel where the clippers are going, and there aren’t a lot of really good treatments on the market for that that are labeled for use in people with HIV.” He also suggested looking at drugs used for peripheral neuropathy in patients with other conditions, such as Lyrica for diabetes, because he believes this drug’s use is helping some patients living with HIV.
- One webcast participant noted that **lipodystrophy in the form of facial wasting** has been the biggest issue: “It continues to be a huge issue for many in terms of stigma, self-esteem, depression, and isolation, and can affect adherence for those currently on meds, and prevent others from starting treatment in the first place.”
- Many participants also discussed whether they believed that HIV can be appropriately described as a “**manageable chronic condition.**” Participants raised several concerns with this term:
 - Considering HIV to be “manageable” may be counter-productive to the advancement of treatments. As one participant expressed, it could “turn the dial down [on finding a

cure]... because now we can move to another disease state that maybe isn't manageable...".

- Labeling HIV as manageable may lower patients' sense of urgency in practicing safe sex or in patients who may think, "I'll deal with it when it's a problem, I don't have to take meds until that time."
- Medication resistance and the long term cumulative effects of HIV therapy (e.g., on the heart and bones) mean that current therapy may not be sustainable, making it difficult to call the disease manageable.
- One participant said the term "irks" her because there are so many factors involved in managing HIV, many not "just medical," such as stigma, fear of rejection, and disclosure.
- However, one participant commented, "When I go see my primary, my HIV is not at the forefront of our conversation. When I go see my infectious disease doctor, my HIV is not the primary conversation. So I take that that it's manageable."

Perspectives on switching medications

Discussion regarding regimen changes highlighted how patients must make critical decisions as to when and/or whether to change the treatment regimen they are currently using. Patients expressed hesitation about changing regimens, especially when their viral load is well-controlled with a current regimen. One participant noted, "... if I change and it doesn't work, then am I using up one of those pools of meds that I have access to?"

One patient noted that he would not switch a currently successful regimen for one that is simpler, but his "pipedream" vision would be a "tailored capacity" to put together the meds he is taking into one pill. Another patient noted that switching would have a strong impact on all the other medications she takes for other conditions, so changing her regimen would be complicated by first having to ensure a new regimen would be compatible with these other meds that are not directly related to her HIV therapy. Another patient shared the view that he would possibly go to a once-a-day pill "at some point in time," but he has essentially become accustomed to taking his medications multiple times per day.

Perspectives on ideal treatment

When asked for their thoughts on how current therapies could improve (i.e., what are patients looking for in an "ideal treatment"), participants commented on the following:

- **Formulations** of potential new products that could help minimize non-adherence were frequently mentioned. Many patients pointed out that an ideal treatment would be a long-acting product that would limit the number of times patients must take a dose. One patient noted that other conditions, such as osteoporosis, have treatments that are only dosed weekly or monthly and asked, "Why can't we get to that for HIV?" Another patient noted that developing treatments for, say, cardiovascular conditions alongside of HIV in a single dosage would "start to address the adherence question."

One patient noted that it is very rare for most people to ever be able to consistently never miss a dose, and therefore it is critical for advancing drug development efforts for pharmaceutical manufacturers to focus on making long-acting treatments. A patient from an advocacy organization cited a survey conducted by his organization in which 60% of patients, which he

described as particularly adept at self-care and perhaps more savvy than typical patients, identified themselves as non-adherent to therapy. This observation prompted his further comment that FDA and the broader health care system should be taking steps to address the non-adherence issue, and determine what would help patients to “pick up the bottles and take the pills.”

- One participant noted that an ideal treatment may not necessarily be a brand new, different drug, but simply another drug that is similar to other existing drugs, that works for a particular patient when **no drugs work for them anymore**. He expressed concern with fewer drugs for HIV being developed now than in the past, noting the “narrowing of the antiretroviral pipeline.” He said that some drugs have been pulled from development because manufacturers may not have perceived enough future profit from “another me-too drug.” However, he explained that such drugs could be of value to “treatment-experienced” patients whose current drugs may no longer be effective and who could possibly benefit from another choice of drug.
- Considering the growing population of patients living with HIV who must also manage other **chronic conditions**, one participant commented that current therapies are typically tested on otherwise healthy subjects, and that he believes it is important to have post-marketing studies to see how FDA-approved medications affect patients who have multiple chronic conditions.
- One participant stressed the need for readily available and accessible therapies, including **supportive therapies** such as massage therapy and acupuncture.

Pediatric perspective on HIV treatments

At the same time that many patients living with HIV are getting older, there is a completely different, and also very significant changing population, the pediatric population. Pediatric patients span a wide range, from neonate to college age. One participant who was specifically representing the pediatric perspective noted several unique considerations for this population:

- **Side effects:** While the occurrence of a side effect like “night terrors” is likely not greater than those in adult patients, its impact and how it is perceived by young people can be much stronger. Gastrointestinal issues related to HIV therapies can also be of much greater concern to a child than to that of an adult who has a more mature outlook. Nausea was noted as a significant factor, especially for school-age children. In addition, the participant noted that long-term effects are more important in this age group, saying, “It’s not always the immediate side effects – you [also] have to think about the bones, the body, and the brain, because those things are all developing at a time they’re taking toxic drugs...”
- **Non-adherence:** It was suggested that some pediatric patients may have a “cavalier” attitude toward adherence, feeling like they do not have to take medication. It was noted that care settings and communication from providers dramatically impact how young patients view adherence to therapy. The participant explained, “how the medication is explained and the support [patients] get while taking medication” really matters.
- **Changing regimens:** Another unique aspect of pediatric patients is that they change regimens frequently. A significant number of pediatric patients therefore have already gone through first-

line and second-line treatment and are now on salvage therapy,⁶ making effective treatment for pediatric patients an important issue.

- **Transitioning to adult care:** As this growing number of pediatric patients transitions into adult care, it will be important for clinicians to understand that many of these patients already have complicated medical histories and that they cannot be treated the same as adults who more recently became infected.
- **Ideal treatment:** From a pediatric perspective, a drug that has fewer side effects and is easy to administer adds to an ideal formulation, such as a drug available in liquid formulation or in a form that can be sprinkled on food.
- **Research lag:** A long lag time still exists before adult ARTs are available for pediatric populations, particularly the neonatal population.

Discussion Topic 2: Patients' perspectives on HIV cure research

The second part of the meeting focused on patient perspectives on HIV cure research. Five panelists (*Appendix 2*) provided comments to start the dialogue. The panelists each had significant experience as HIV patient advocates. Several were also patients living with HIV, who had personal experience as participants in a wide variety of clinical trials on HIV therapies.

The discussion and polling questions demonstrated that many participants had direct experience in participating in clinical trials for drugs being tested for HIV therapy. One participant described participating in “dozens of clinical trials.” This participant commented that “despite my highly resistant virus, I’ve been undetectable for over 5 years now... so I believe I’m really here as a result of being in clinical trials and aggressive approach to fighting HIV from the very beginning.”

In contrast, few participants said that they had experience in trials specific to HIV cure research. They indicated that patients’ perspectives on HIV research may differ from their perspectives on research conducted in “early days.” As one participant commented, “...we are at a very different place today...”

Through the panel comments and facilitated discussion, participants indicated that many patients living with HIV have a sincere and significant interest in participating in clinical trials for general HIV research, and that often their interest is motivated by both altruistic and personal reasons. When asked through a polling question for participants, more than half indicated they would consider participating in a clinical trial related to cure research even if there were no direct benefit for them.

Throughout this discussion, one participant discussed results of a recent survey he conducted with another HIV advocate on HIV cure research participation (referred to here as the “cure studies” survey). Over 2,000 HIV patients completed the survey. This participant reported that 88% of survey respondents reported having at least a level of “somewhat motivated” or higher to participate in cure studies. 24%

⁶ A last line of defense against HIV infection that has developed resistance to standard treatment; it often has much more severe side effects than standard therapy, and if salvage therapy is not effective, there may be no other life-saving treatments available to the patient.

reported being “very motivated” to participate. This participant also noted that the survey showed similar results even when respondents were told that the research “definitely would not benefit them.”

Motivation to participate in cure research studies

Participants were first asked to consider why patients may be interested in participating in cure research studies, particularly in cases when a study is not expected to provide a direct health benefit to the study participant.

- **Altruism** received the most attention in the discussion. Participants explained that some patients are genuinely willing to participate simply for the greater good of the HIV community and society. A participant noted, “In the gay community it’s known that people want to give back in the form of clinical research to help their own.” However, participants also expressed caution in interpreting perceived altruism as a primary motivation for participation in cure research. They described an overlap between altruism and unavoidable desire for personal benefit. The participant who described the “cure studies” survey results noted that people who were “very motivated for altruistic reasons” were also “very, very motivated to benefit themselves.” This participant concluded that “...if we’re depending on people’s altruism, we also have to be very careful not to in any way play on any misperceptions they may have that they are going to benefit from a study when they actually won’t.” Another participant expressed concern that while “altruism is a wonderful thing... and most people have it,” that when people stop to think about the “the reality of the trial,” including the risks and impact on family, job and current treatment, that “those are all those considerations that may make a difference.”
- Several participants commented on perceived **indirect health benefits** that could influence decisions about participating in trials, including potential “improvement in immunology and immunologic response” or “more monitoring and [a] deeper dive into what’s functioning inside my body than I would get if I just go to my HIV doc.”
- A few participants described a desire to contribute to the development of treatments that could **help “your future self”** several years down the road.
- A few participants commented that many patients have a perception that if they “**get [their] foot in the door**” with an early trial, that they’ll “be in line for something that really will be beneficial two steps down the line.” One participant cautioned however, that in many cases, participation in an early trial disqualifies the patient from participating in the next step.
- A few participants noted that in some cases, people may be motivated to participate in a trial simply for the **financial compensation** provided. One cautioned that in such cases, it is very important to clearly inform these patients of risk associated with the trial.

Perspectives on risks of cure research studies

Participants were also asked to describe how they might consider the potential risks of participating in a cure research study. In the discussion of risks, participants raised several key points, noted below:

- **Immediate vs. long term risk:** Some participants viewed the short-term, immediate risks, such as nausea, vomiting, and diarrhea, as more worrisome than the long-term risks, such as the possibility that an experimental treatment could at some point lead to harm, such as cancer, in the future. Participants explained that their decision would be more likely to be made based on the short-term impacts as opposed to the long-term risks. As one participant described, “...we’ve all sort of experienced, ‘Oh, you could die.’ I was told when I was diagnosed that I had 6 months to live, and here it is nearly 30 years later fortunately, but I think it’s sort of the down the road kinds of things I’m willing to take some risks on, more so than I am my quality of life now.” A participant, with regards to thinking about risks, said “... you are not willing to subject yourself to that hurdle anymore for any particular reason without you getting a guarantee.”

Although this seemed to be the prevailing view, there were others who expressed the idea that they would be willing to endure some short-term discomfort, if it would help others, but that if the experimental drug might cause long-term serious harm, it might change their willingness to help others by participating in the trial.

- **“How much is too much risk?”:** When asked if there would be any circumstances of a trial that might make participation “too risky,” some meeting participants seemed to agree that there is much diversity in cure research and that even for the riskiest of trials, patients should be able to choose and decide for themselves if they would be willing to participate. However, one participant, when asked by an FDA panel member if there is a “safety threshold” beyond which FDA should not allow trials to move forward, responded by saying that he would be uncomfortable with a trial that would lead to “anything below 500 as a CD4 count.” He expounded by saying he would “prefer that we don’t allow people with high Framingham risk scores⁷ to enter these studies.” He also expressed concerns with studies that would result in “treatment interruptions longer than 16 weeks.”
- **Risk communication:** The discussion underscored a diversity of viewpoints on the subject of motivation for participation and that a decision to participate is highly individual and personal and likely to be widely different from one person to the next. As risk was discussed, patients frequently stressed the importance of making the decision based on whether they believed the risk was clearly communicated, a topic that was much more fully discussed later in the day in the context of informed consent (see, “perspectives on informed consent,” p. 14).

Several participants commented on the fact that the patients present at this particular meeting were not representative of the broad HIV community. It was noted that a wide range of “class, race, sexuality, gender, etc., have an impact” on the types of risks people are willing to accept.

Willingness to give up a current regimen to participate in a trial

For some clinical trials, patients must stop their current treatment regimens in order to take the experimental therapies being tested. Faced with the question of how they might handle this decision, patient response varied. Discussants agreed that individual circumstances come strongly into play. For instance, someone who is well-established on a regimen and has been undetectable for a prolonged

⁷ The Framingham risk score is a calculation that estimates the 10-year cardiovascular risk of a patient.

period of time may be much more reluctant to give up treatment compared to a patient who is not well-controlled and is not risking the safety of a stable regimen.

A polling question on this topic showed ambivalence among meeting participants as to whether or not they would be willing to give up their regimen to participate in a trial, with a relatively even mix of those who would, those who would not, and those who were not sure.

Several meeting participants reflected the range of perspectives through their comments. As one participant shared, “I think being asked to give up my treatment regimen that I’ve worked very hard to get something that works, number one, and two, doesn’t interrupt my daily flow, is a real barrier in terms of participating in cure research... I’ve taught myself over many, many years how to stay adherent, and to change that whole regimen up might be difficult for me to make that leap.” Another participant described his experience with a vaccine trial, which required a treatment interruption. Afterwards he had to add more medications to make him undetectable again; “but even given that,” he stated, “I think it’s well worth it.”

In contrast, the participant who conducted the “cure studies” survey reported that respondents indicated that when making decisions to participate in a clinical trial “whether they felt great about their therapy or didn’t like it, it didn’t seem to matter.” In addition, the survey found that “people who had been positive the least long, who had the highest CD4 count, were the least likely to take part in these kinds of studies.”

Perspectives on informed consent

HIV cure research also raises challenges related to the informed consent process. At the meeting, FDA sought patient input on how potential benefits and risks of HIV cure research can best be communicated to prospective study participants.

Many participants believed that patients must be better and more clearly informed of the risks and benefits and other implications of participating in a cure research clinical trial. This includes clearly stating when there is “no immediate known benefit” to the study participant, how participation in one stage of research affects the ability to participate in future stages of the research, and when treatment interruption is “not consistent with federal guidelines” for treatment of people with HIV.

More broadly, many participants also discussed that informed consent documents have become lengthy and highly complex. For example, one participant described, “I would really want to know the benefits... and the risks... without having to go through a 5-hour process with 9,000 different pages of something I didn’t necessarily understand.” Some participants noted that some informed consent processes seem to primarily serve the purpose of preventing liability for the study investigators, as opposed to presenting clear information of risk and benefit to the potential subject. This led to rich discussion of how information could be more clearly communicated and opportunities for improving the process:

- Participants were in broad agreement that technology could play a key role in a solution, specifically by providing other ways of informing patients outside of the printed word. One participant noted that at jury duty, they showed a video of the information he needed to know about being a juror, and he thought a similar technique of using video to inform patients could

be readily transferable to the informed consent process. There was wide agreement among participants that this idea offered strong potential to a solution.

- One participant pointed out that the two words “process” and “counseling” are important when it comes to informed consent. He recognized how busy clinicians are, but asked, “Why can’t we make this a counseling effort that really goes in depth with these protocols?”
- Many participants agreed that the idea of a “post-test,” to confirm that patients understood the information presented to them, would help ensure patients are adequately informed. However, one participant offered the idea to not use the word “test” per se, but to call the activity something less intimidating, such as an “assessment.”
- One participant introduced the concept of a “peer navigator,” someone who has been through a trial before who talks to a potential participant, to engage people to get into trials, and who provides “some sort of peer support system... to keep them engaged.”
- One participant suggested that broader reach of community education would be helpful; for instance, consideration of developing a community advisory board in communities where research will be conducted, and other ways of educating the public about informed consent in general, as opposed to focusing only on the informed consent of a particular trial.

Discussion of the word, “cure”

Meeting participants were asked to react to the word “cure” with regard to overall efforts in what is frequently called “HIV cure research.” Their responses indicated a wide range of views that included agreement that other words besides the word “cure” may merit consideration.

One participant reflected that the term could lower perceptions among patients and possibly encourage them to be more lax in their use of current therapies or stop taking them altogether. He said he agrees that perhaps some “other nomenclature should be used” because he “gets discouraged every time I hear the ‘C word’ used” and that it may lead to false hope, because a cure may not be within reach for a long time.

Another participant related the word “cure” to the important issue of informed consent and reiterated that any kind of study with the word “cure” in it should include careful consideration for how the study investigators inform a patient of realistic expectations of the study’s results.

Summary of comments submitted to the docket

Thirteen comments were submitted to the public docket that supplemented the June 14 Patient-Focused Drug Development meeting. The majority of docket comments were submitted by HIV patients, primarily “long-term survivors” who also identified themselves as patient advocates. One comment included unpublished results of a 2012 survey of approximately 450 Dutch persons living with HIV on the topic of a potential HIV cure, which is referenced here as the “Dutch survey.” One comment was submitted by the patient advocate who provided the pediatric perspective at the meeting.

The submitted comments largely supported the perspectives shared by participants at the June 14 meeting. They also provided additional context to supplement the meeting input. The following is a summary of the submitted docket comments.

Perspectives on current HIV treatment

A few commenters reiterated the perspectives shared in the meeting on the side effects and downsides of medication. One noted wild dreams as a troublesome side effect. Several comments echoed what was heard at the meeting regarding the challenges of treating patients with comorbid conditions, particularly as the HIV patient population ages. One commenter described symptoms due to aging, such as visceral adipose tissue redistribution, arthritis, and bone fractures. This commenter concluded that “there is a greater need to understand the impacts of the virus as we age,” particularly the relationship between HIV and cancer, cardiovascular incidents, diabetes, and cognitive function.

The comment submitted by the pediatric advocate reiterated the need for new drug formulations, better route of administration, understanding of the drug’s effect on the child’s body, and more rapid availability of adult treatments for use in pediatric populations. The comment noted that “side effects typically occur during critical periods in a child’s growth and development, compromising the patient’s overall health and wellbeing in different ways than in the adult population.” The comment explained how pediatric treatment adherence is an issue due to strict dosing schedules and the drugs’ taste and texture. The comment also highlighted the challenges of drug resistance among pediatric patients.

Perspectives on the impact of HIV on daily life

Several commenters reiterated the impact that the physical and psychosocial impacts of the disease and its treatment have on HIV patients’ daily life. In the Dutch survey, respondents identified the top five disadvantages of HIV as: “risk of getting side effects or health problems in the future,” “negative impact on health,” “risk of infecting others,” “stigmatization,” and “side effects from medications.” Stigma was highlighted by a few other comments. As one described, “Stigma is still one of the most critical issues faced by people living with HIV.”

Perspectives on ideal treatments

A few commenters stressed the need for drugs with fewer side effects, lower cost, and flexible dosing schedules to improve adherence to medication. Several comments stated a strong need to focus more attention on HIV patients already on salvage therapy, and a need to develop new medications with differing modes of action for lasting viral suppression in these patients and for patients with multi-drug resistant HIV. In such cases, once the salvage therapy starts to fail, there are no treatment options for such patients. One commenter noted that research should be focused on treatment-experienced patients, along with those recently infected or treated early. It was also stressed that there is a need to focus studies on patients who have CD4 counts lower than 300, even after being on treatments for several years.

Perspectives on cure research

Several comments focused on participation in HIV cure research and informed consent. Below are highlights from these comments:

- Perspectives on an HIV cure in general:** A few commenters reflected more globally on the benefits and downsides of achieving a cure for HIV. For example, the commenter who submitted the Dutch survey reported that although 86% of respondents rated their physical health over the past month as being “reasonably good” or better, 94% indicated that a cure is “very” or “somewhat” important to them. However, the survey results suggest that the type of cure matters. Based on the results of the Dutch survey, this commenter believed that there is a disconnect between researchers who target a “functional” cure and patients who desire a “complete” cure, given the significant impact that stigma, risk of transmission, and other psychosocial effects have on patients’ lives. Another commenter believed that unless a cure fixes transmission and re-infection, HIV and its associated problems will not be addressed.
- Perspectives on the benefits and risks of cure research trials:** A few commenters offered perspectives on various reasons HIV patients may be motivated to participate in an HIV cure research study. One, who participated in a recent Phase I trial, described his personal satisfaction that “I was part of something big on behalf of future generations.” This person indicated that he was aware that there was no expected clinical benefit for participants in the study. However, as was heard in the meeting, this commenter and others stressed the importance of making sure that prospective study participants are fully informed of all potential risks and benefits.
- Perspectives on the word “cure”:** A few commenters specifically reiterated the importance of clear terminology regarding cure research. One commenter noted that the “overarching concern in HIV *cure* research is the potential for the term itself to create the misconception that participation in a trial will lead to an individual being cured.” The commenter who submitted the Dutch survey also suggested clearly specifying the desired outcome of the research (e.g., whether it might contribute to a “sterilizing cure” versus a “future situation... where the body keeps the virus under control”).
- Willingness to give up a current regimen to participate in a trial:** One commenter noted that ART interruptions in cure research require careful review and oversight. It was stressed that ART interruptions may be necessary to participate in a research trial, but that risks such as morbidity and mortality need to be considered as well. Another stressed the importance of having the patient’s physician take part in the decision.
- Perspectives on informed consent:** Several commenters noted that the informed consent process should clearly inform patients about the potential risks and benefits of participating in a trial, particularly when there may not be potential gains. It should also be stated in the informed consent that the purpose of the study is to gather information for future developments. One commenter believed informed consent should also state that researchers have limited understanding of future impacts and how participation in the study would affect participation in future studies. A few commenters offered suggestions on how to improve this communication, for example, by having a “peer or somebody that can relate to the potential participant and explain in detail the pros and cons of the research study.”
- Pediatric perspective:** The comment that focused on pediatric aspects of drug development noted that “the infant immune system might provide a less complex target for HIV cure research that can reveal clues for cure strategies in adults.” The comment stated that anecdotally,

pediatric patients and their parents have expressed interested in participating in cure research trials, noting that “they have the most to gain.”

Other Comments Submitted

- **Awareness and social media:** One comment stressed the need to utilize social media tools to “give an opportunity for people with HIV/AIDS to speak out about living with the condition, and also promote positive outcomes of long-term survivors.”
- **Cost of treatment:** The cost of treatment and the lack of coverage for over-the-counter and alternative medicine were raised in one comment. The commenter noted that long-term cost of providing therapy can be a barrier, questioning the potential cost of any cure. The commenter concluded that “the best hope we have to cure HIV today is to prevent new infections, test unilaterally and link individuals to treatment and supportive care.”
- **Vaccines:** One commenter noted that the development of vaccines that are responsive to circulating HIV strains in global settings should be encouraged. Another comment expressed that it is concerning that “the bar for therapeutic vaccines is higher since ARVs are so successful at lowering viral load” and therapies, i.e. vaccines, should be cleared based on proven safety and efficacy, and not based on what is available in the market.
- **Global impact:** A commenter highlighted “the impact of the meeting beyond the borders of the U.S. where national institutions fund and carry out the greater share of current HIV research.” It was stressed that “disparity, barriers to inclusion, problems with capacity to address populations in need and lack of engagement with global populations most affected by HIV should also form grounding principles of FDA’s response to cure research issues.”

Conclusion

This meeting underscored the rapidly changing demographic and the range of perspectives of the patient population affected by HIV. The input provided by patients highlights the need for improved therapies and better informed consent processes, and the diversity of patient perspectives on HIV cure research. FDA is grateful to the patients and advocates who courageously shared their experiences and perspectives through the Patient-Focused Drug Development meeting and public docket. This effort has enabled us to obtain, in a systematic way, patients’ points-of-view on the impact of HIV on daily life, current therapies, and HIV cure research. We recognize that patients have a unique ability to contribute to our understanding of the broader context of this disease, which is important to our role and the role of others in the development of safe and effective drug therapies for HIV.

Appendix 1: Meeting Agenda and Discussion Questions



Meeting on HIV Patient-Focused Drug Development and HIV Cure Research



June 14, 2013

8:30 – 9:30 am	Registration
9:30 – 9:40 am	Welcome Edward Cox, MD, MPH <i>Director, Office of Antimicrobial Products, Center for Drug Evaluation and Research (CDER), FDA</i>
9:40 – 9:50 am	Overview of FDA’s Patient-Focused Drug Development Initiative Theresa Mullin, PhD <i>Director, Office of Strategic Programs (OSP), CDER, FDA</i>
9:50 – 10:00 am	Background on Current HIV Treatment Kimberly Struble, PharmD <i>Clinical Team Lead, Division of Antiviral Products, CDER, FDA</i>
10:00 – 10:10 am	Overview of Discussion Format Sara Eggers, PhD <i>Office of Program and Strategic Analysis, OSP, CDER, FDA</i>

Discussion 1: Patients’ Perspectives on Current Approaches to Managing HIV and on Symptoms Experienced Because of HIV or Its Treatment

10:10 – 10:30 am	Panel #1 Comments on Questions 1 – 3 (See Appendix) A panel of patients and patient representatives will provide comments to start the discussion.
10:30 – 11:00 am	Large-Group Facilitated Discussion on Questions 1 – 3 Patients and patient representatives in the audience are invited to add to the dialogue.
11:00 – 11:15 am	Break
11:15 – 11:30 am	Panel # 1 Comments on Questions 4 – 5 (See Appendix)

11:30 – 12:00 pm	Large-Group Facilitated Discussion on Questions 4 – 5
12:00 – 12:15 pm	Discussion with FDA Panel An FDA panel will have an opportunity to comment on any points raised in the facilitated discussion or field any relevant questions from the audience.
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12:15 – 1:30 pm	Lunch
1:30 – 1:35 pm	Afternoon Opening Comments Janet Woodcock, MD <i>Director, CDER, FDA</i>
1:35 – 1:40 pm	Summary of Morning Discussion Richard Klein <i>Director, Patient Liaison Program, Office of Health and Constituent Affairs, Office of the Commissioner, FDA</i>
1:40 – 1:50 pm	Background on HIV Cure Research Ilan Irony, MD <i>Chief, General Medicine Branch, Division of Clinical Evaluation and Pharmacology/Toxicology, Center for Biologics Evaluation and Research, FDA</i>
1:50 – 2:00 pm	Informed Consent Issues in HIV Cure Research Sara Goldkind, MD, MA <i>Senior Bioethicist, Office of Good Clinical Practice, Office of the Commissioner, FDA</i>
2:00 – 2:05 pm	Overview of Discussion Format Sara Eggers, PhD <i>Office of Program and Strategic Analysis, OSP, CDER, FDA</i>
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Discussion 2: Patients' Perspectives on HIV Cure Research

2:05 – 2:35 pm	Panel #2 Comments on Questions 1 – 4 (See Appendix)
2:35 – 3:25 pm	Large-Group Facilitated Discussion on Questions 1 – 4
3:25 – 3:40 pm	Break
3:40 – 4:00 pm	Panel #2 Comments on Questions 5 – 6 (See Appendix)
4:00 – 4:35 pm	Large-Group Facilitated Discussion on Questions 5 – 6

4:35 – 4:50 pm

Discussion with FDA panel

4:50 – 5:20 pm

Open Public Comment

5:20 – 5:30 pm

Closing Remarks

Theresa Mullin, PhD

Director, OSP, CDER, FDA

Discussion Questions

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?

Appendix 2: Meeting Panel Participants

Topic 1

- Patient Panel
 - David Brakebill
 - Melanie Reese
 - Joseph Jefferson
 - Catherine Connor

- FDA Panel
 - Theresa Mullin, Office of Strategic Programs, CDER
 - Ed Cox, Office of Antimicrobial Products, Office of New Drugs, CDER
 - Debra Birnkrant, Division of Antiviral Products (DAVP), CDER
 - Adam Sherwat, DAVP, CDER
 - Celia Witten, Office of Cellular, Tissue, and Gene Therapy, CBER
 - Ilan Irony, General Medicine Branch, Division of Clinical Evaluation and Pharmacology/Toxicology, CBER

Topic 2

- Patient Panel
 - David Evans
 - Murray Penner
 - Jeff Taylor
 - Lynda Dee
 - Matt Sharp

- FDA Panel
 - Ed Cox, Office of Antimicrobial Products, Office of New Drugs, CDER
 - Debra Birnkrant, DAVP, CDER
 - Jeffrey Murray, DAVP, CDER
 - Kimberly Struble, DAVP, CDER
 - Adam Sherwat, DAVP, CDER
 - Damon Deming, DAVP, CDER
 - Celia Witten, Office of Cellular, Tissue, and Gene Therapy, CBER
 - Ilan Irony, General Medicine Branch, Division of Clinical Evaluation and Pharmacology/Toxicology, CBER
 - Sara Goldkind, Office of Good Clinical Practice, Office of the Commissioner

Appendix 3: Meeting Polling Questions

The following questions were posed to in-person and web meeting participants at various points throughout the June 14, 2013 HIV Patient-Focused Drug Development meeting. Participation in the polling questions was voluntary. The results were used as a discussion aid only and should not be considered scientific data.

Demographic Questions

1. Do you live within the Washington D.C. metropolitan area or outside of the Washington D.C. metropolitan area?
 - a. Washington, D.C. metropolitan area (including the Virginia and Maryland suburbs)
 - b. Outside of the Washington, D.C. metropolitan area

2. What is your age?
 - a. Younger than 25
 - b. 25 – 34
 - c. 35 – 44
 - d. 45 – 54
 - e. 55 – 64
 - f. 65 or greater

3. Are you:
 - a. Male
 - b. Female
 - c. Transgender
 - d. I'd prefer not to answer

4. Have you been diagnosed as having HIV?
 - a. Yes
 - b. No

5. For persons living with HIV: how long ago was your diagnosis?
 - a. Less than 2 year ago
 - b. 2 years ago to 10 years ago
 - c. 10 years ago to 20 years ago
 - d. More than 20 years ago
 - e. I am not a person living with HIV

Questions for Topic 1

1. For persons living with HIV: How many different types of antiretroviral treatment (ART) regimens have you taken?
 - a. I have never taken any ARTs.
 - b. I am currently on my first regimen.
 - c. I have taken 2-3 different regimens.
 - d. I have taken more than 3 different regimens.
 - e. I'm not sure.

2. For persons living with HIV, who take multiple HIV medications: which of the following statements best reflects your overall perspective on having to take multiple HIV medications every day for the rest of your life?
 - a. Overall, it does not have a significant impact on my daily life.
 - b. It does have a significant impact on my daily life, but I feel that I am able to take my medications every day as prescribed by my doctor.
 - c. It does have a significant impact on my daily life, and I am worried that I may not be able to take my medications every day as prescribed by my doctor.
 - d. I'm not sure which or if any of these statements reflects my perspective.

3. For persons living with HIV: Of all the symptoms you experience because of your HIV infection or the treatments you take to manage your HIV infection which of the following symptoms do you consider to have the most significant impact on your daily life? Please choose up to three symptoms.
 - a. Pain, such as head, nerve, muscle or joint pain
 - b. Depression or anxiety
 - c. Stomach or gastrointestinal (GI) issues, such as chronic constipation or diarrhea
 - d. Shortness of breath or other respiratory problems
 - e. Body changes, such as weight loss, or redistribution of fat on the body
 - f. Other symptoms not mentioned
 - g. None of these symptoms affect me

4. For persons living with HIV: Besides antiretroviral therapies (ART), what other therapies are you taking to manage any symptoms you experience because of your HIV or your HIV medications. Check all that apply.
 - a. Medications to help manage sleep
 - b. Medications to help manage pain
 - c. Medications to help manage depression
 - d. Medications to help with stomach or gastrointestinal (GI) issues
 - e. Hormone therapy
 - f. Dietary modifications, such as herbal or nutritional supplements and food restrictions.

- g. Non-drug therapies, such as massage therapy, meditation, acupuncture
- h. Other therapies not mentioned
- i. I'm not taking any additional therapies

Questions for Topic 2

5. Have you ever participated in any type of clinical study related to HIV?
 - a. Yes
 - b. No
 - c. I'm not sure

6. Have you ever participated in any type of clinical study specifically related to HIV cure research?
 - a. Yes
 - b. No
 - c. I have participated in a clinical study, but I'm not sure if it was specifically related to HIV cure research.

7. For persons living with HIV: Would you consider participating in a research study if it was unlikely that you would gain any direct health benefits from participating?
 - a. Yes, I would consider participating in a study
 - b. No, I would not consider participating in a study
 - c. I'm not sure

8. For persons living with HIV: Would you consider participating in a research study if it meant that you had to temporarily stop taking your current HIV-medications?
 - a. Yes, I would consider participating in a study
 - b. No, I would not consider participating in a study
 - c. I'm not sure

9. For all patients and patient representatives: Do you think it would be appropriate for clinical study participants to take a post-test at the end of the informed consent process, to make sure that they understand the most important aspects of the study?
 - d. Yes
 - e. No
 - f. I'm not sure

Appendix 4: Sample Benefit-Risk Framework for HIV

Introduction

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics.⁸ The Benefit-Risk Assessment Framework involves assessing five key decision factors: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, *Risk*, and *Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the Framework, the *Analysis of Condition* and *Current Treatment Options* rows summarize and assess the severity of the condition and therapies available to treat the condition. This assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the HIV Patient-Focused Drug Development meeting and docket comments helps further our understanding of the *Analysis of Condition* and *Current Treatment Options* for this disease.

The information in the top two rows of the sample framework on the next page draws from various sources, including patient and patient representative input from the HIV Patient-Focused Drug Development meeting held on June 14, 2013. This sample framework contains the kind of information that we anticipate could be included in a framework completed for a drug under review for HIV infection. This information is likely to be modified over time based on a further understanding of the condition or changes in the treatment armamentarium.

⁸ Commitments in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) include further development and implementation of the Framework into FDA's review process. Section 905 of the FDA Safety and Innovation Act also requires FDA to implement a structured benefit-risk framework in the new drug approval process. For more information on FDA's benefit-risk efforts, refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

Sample Benefit-Risk Framework for HIV: Analysis of Condition and Current Treatment Options

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> – There are more than 1.1 million people in the U.S. living with HIV and approximately 50,000 new HIV infections each year. – Patients infected with HIV experience a range of symptoms depending on the stage of their infection spanning from initial acute infection, latent infection, early symptomatic HIV infection, and finally progression to AIDS, if left untreated. – For the majority of patients, the symptoms are well-controlled with ARTs, however for a subset of patients symptoms are severe and significantly impact their daily lives. – Physical symptoms experienced at various stages often include fever, fatigue, swollen lymph nodes, muscle soreness, diarrhea, weight loss, coughing and shortness of breath, joint pain, inflammation, night sweats, peripheral neuropathy, and lipodystrophy. – The disease can also have a substantial psychosocial impact on patients’ daily lives including stigma, issues with self-esteem, depression, and isolation. – <i>Refer to the Voice of the Patient report for a more detailed narrative.</i> 	<p>HIV/AIDS is a serious disease and poses several public health challenges in the United States. It is a disease with slow progression from acute infection to AIDS.</p> <p>Overall, the progression and symptoms of HIV are well-controlled with a wide range of medications. However, the physical and psychosocial symptoms can have serious impacts on patients’ quality of life, some of which include stigma, issues with self-esteem, and depression.</p>
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> – There is no cure for HIV. Anti-retroviral therapy (ART) is a combination drug therapy used to control HIV. FDA-approved drugs fall under five drug classes, some of which include non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, and protease inhibitors. – ARTs are the most effective treatments in managing the disease and preventing progression to AIDS. They help increase life expectancy in those infected with HIV and reduce the risk of HIV transmission. – Side effects of ARTs may be short or long-term, and vary depending on the type and combination of medications. Side effects may include nausea, vomiting, diarrhea, lipodystrophy, decrease in bone density, and insulin resistance. Treatment side effects can have significant impact on a patient’s daily life. – Other treatment challenges include life-long adherence to ART, tolerability issues, scheduled dosing, development of drug resistance, and psychosocial impacts. – Emerging research is exploring new ways to either clear HIV from the body or control the virus without ART. – <i>Refer to the Voice of the Patient report for a more detailed narrative.</i> 	<p>HIV is a condition that requires life-long anti-retroviral therapy. Although HIV is manageable with FDA-approved drugs, they have short and long-term side effects that can have significant impact on patients’ daily life. These side effects may also be a barrier to starting or continuing HIV medications.</p> <p>Maintaining treatment adherence is a challenge for patients. Adherence is important in preventing drug resistance, and slowing the progression of HIV to AIDS.</p> <p>Continued research, including clinical trials, is essential to find a treatment to eliminate HIV infection. Potential clinical trial participants must carefully weigh their reasons for wanting to participate against the often highly uncertain risks of the study.</p>