

# MK-0518 Expanded Access Program

Investigational HIV therapy in the  
Massachusetts Correctional System

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# HIV in the Correctional Setting

- U.S. prison populations was over 2.2 million at the end of 2005.
- 1.8% of inmates are known to be HIV-positive.
- It has been estimated that each year about 25% of all patients with HIV spend some time in the correctional setting.

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### HIV–AIDS among Prison Inmates at the End of 2004.\*

Jurisdictions with the Most Prisoners Living with HIV–AIDS	No. of Inmates Living with HIV–AIDS	Prevalence of HIV–AIDS %
New York	4500	7.0
Florida	3250	3.9
Texas	2405	1.7
Federal system	1680	1.1
California	1212	0.7
Georgia	1109	2.2

\* Data are from Maruschak.<sup>2</sup>

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# HIV care in the Massachusetts Correctional System

- Dedicated RN case managers run the clinic at each facility.
- Infectious diseases physicians provide on-site consultation on a weekly to monthly basis depending on the volume of patients.
- Inmates go through a central facility, MCI-Concord, where they await sentencing and classification.

# Multi-drug resistant HIV in the Massachusetts Correctional System

- Because MCI-Concord is the intake facility, patients frequently arrive from the community, where they have been non-compliant with medications.
- An initial case of MDR-HIV was seen in 4/06, requiring T-20 to construct a successful three-drug regimen.
- In 10/06, two men additional men presented with multi-drug resistant HIV.

# Multi-drug resistant HIV in the Massachusetts Correctional System

- Because of the increase in highly-resistant disease, the patients' genotypes were reviewed by an expert at Brigham and Women's Hospital, Dan Kuritzkes, MD, President of the HIV Medical Association.
- Dr. Kuritzkes recommended that consideration be given to one of three new investigational agents that became available through expanded access programs in fall 2006.

# Recent History of HIV Therapeutics Research in the Correctional Setting

- There has been a long history of debate surrounding the conduct of clinical trials in correctional settings.
- In the 1990s, several universities and correctional systems had programs, which provided investigational HIV medications to prisoners.
- In 1998, a pharmaceutical company offered a non-comparator trial of triple nucleoside therapy for the treatment of HIV in a protocol that was designed to recruit prisoners, but no community patients.

# Current State of HIV Therapeutics Research in the Correctional Setting

- Prison advocates expressed concern about the trial because all three medications were already available outside of the research setting and preliminary data showed that triple-nucleoside therapy might be inferior to NNRTI or PI-based regimens.
- Ultimately, in 2001, the Office of Human Research Protections found the trial to be unethical and found the IRBs at several major institutions to have inadequate protection for prisoners.
- Since then, there have been virtually no clinical trials involving HIV investigational pharmaceutical agents in the state prison systems.

# Institute of Medicine Report

- In July 2006, the Institute of Medicine published a report, “Ethical Considerations for Research Involving Prisoners” that recommended specific protections for prisoners involved in research.
- One key tenet of the report was “to shift from a category-based to a risk-benefit approach to research review.”

# HIV Salvage Therapy

- Fuzeon® (T-20, enfuvirtide) received FDA approval in March 2003.
- It was the first drug with a new mechanism of action to gain FDA approval since nevirapine in 2/96.
- T-20 is administered twice daily by injection, with painful subcutaneous nodules commonly occurring at injection sites.
- Compliance is low, both within and outside of the correctional setting.
- Transition to the community can be complex and the barrier to mutation is relatively low.

# HIV Salvage Therapy

- While several new protease inhibitors of have been developed since 2003, highly-experienced patients may have mutations that decrease the usefulness of these agents.
- In fall of 2006, two new classes of agents for anti-retroviral therapy were offered as expanded access options: CCR5-inhibitors (Maraviroc®) and integrase inhibitors (MK-0518).
- In addition, a third agent, TMC-125, was made available. This drug is an NNRTI that can be used in the setting of common mutations (K103N, Y181C) that decrease responsiveness to other agents in this class.

# Decision to Apply for MK-0518

## Expanded Access

- The two inmates were informed that they had highly drug-resistant HIV.
- In order to make an adequate three-drug regimen, the first inmate would need either T-20 or an investigational agent.
- The options were explained to the inmate in detail prior to submitting the application for MK-0518.
- The inmate understood the risk of an investigational agent, but preferred that risk to the known side effects associated with T-20.

# Decision to Apply for MK-0518 Expanded Access

- The second inmate had an HIV virus that was fully resistant to all available protease inhibitors and nucleoside reverse transcriptase inhibitors.
- He had a history of a life-threatening Stevens-Johnson reaction to Efavirenz.
- He would need T-20 and an investigational agent or **two** different investigational agents to make an adequate three-drug regimen.
- This patient was also interested in MK-0518 and preferred this option to a regimen including T-20.

# Establishment of MK-0518 Expanded Access Program (EAP)

- Dr. Joseph Cohen, director of the IRB, and Dr. Arthur Brewer, director of UMass Correctional Health were contacted about the feasibility and appropriateness of setting up the MK-0518 EAP.
- Dr. Brewer worked closely with Terre Marshall, Director of Health Services for the Department of Corrections to address their concerns regarding the study.
- Without the cooperation of the IRB, correctional health and the department of corrections, the program would not be able to take place.

# Clinical Trial Phases

- **Phase I:** Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- **Phase II:** The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
- **Phase III:** The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.
- **Phase IV:** Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use.

<http://www.nlm.nih.gov/services/ctphases.html>

# Expanded Access Programs

- “The primary intent of a treatment IND/protocol (expanded access) is to provide for access to the new drug for people with a life-threatening or serious disease for which there is no good alternative treatment.”
- “Expanded access protocols can be undertaken only if clinical investigators are actively studying the new treatment in well-controlled studies, or all studies have been completed. There must be evidence that the drug may be an effective treatment in patients like those to be treated under the protocol. The drug cannot expose patients to unreasonable risks given the severity of the disease to be treated.”

<http://www.nlm.nih.gov/services/faqctgov.html>

# HIV Salvage Therapy: Comparison of new Expanded Access Agents

## ■ MK-0518

- New class of agent; acts at novel site. Blocks integration of virus into host DNA.
- No special laboratory requirements.
- Likely to be useful in late stage patients with longstanding infection.

## ■ Maraviroc®

- New class of agent; acts at novel site. Blocks CCR5 binding.
- Requires tropism assay and other samples that must be frozen to  $-70^{\circ}\text{C}$ .
- In later phases of HIV infection, the virus changes its target receptor from CCR5 to CXCR4.

# HIV Salvage Therapy: Comparison of new Expanded Access Agents

- TMC-125
  - Acts as NNRTI, but still effective in presence of some NNRTI mutations.
  - No special laboratory requirements.
  - Useful in late-stage infections, but effectiveness decreases as number of NNRTI mutations increases.

# HIV Salvage Therapy – Importance in the Correctional Setting

- Inmates with MDR-HIV can spread the disease within the institution and to the community once released.
- When these individuals are released, they frequently have difficulty accessing care in the community.
- The correctional setting offers a unique opportunity to bring HIV infection under control, with the hope that this control will be sustained upon re-entry.
- Risk of death with uncontrolled AIDS is high.
- Treatment costs for patients with uncontrolled AIDS are high as well.

# HIV-HCV Co-infection Clinic Model

- Massachusetts Department of Corrections had pre-existing model – a highly successful co-infection clinic that brings state-of-the-art hepatitis C treatment to HIV-HCV infected individuals.
- The director of the clinic, Dr. Barbara McGovern, and the treatment program served as models for the HIV Expanded Access Program.
- Other institutions may wish to explore existing successful models in establishing new programs.

# Key Elements in Developing an HIV Expanded Access Program

- Links to academic and research institutions in the community to provide guidance and inspiration.
- Support of both correctional health and Department of Corrections personnel in the system.
- IRB chairman and key stakeholders who are open to new ideas.
- Leverage the expertise and example of existing programs in the creation of the new program.
- Assistance from the clinical trial administrator and pharmaceutical company.
- A strong back and thick skin.

# Status Report

- Massachusetts Department of Corrections site received approval to enroll participants in the MK-0518 Expanded Access program from Merck on March 13, 2007.
- Because the number of potential participants had increased from two to six, enrollment has been delayed pending full IRB approval – meeting April 23, 2007.
- This time period will be used to work out details of pharmacy protocol and train nursing staff.
- Plan to submit application for TMC-125 expanded access is underway.