One of the most important contributions that NIAID has made in the area of HIV/AIDS research has been to give its full support to the discovery and development of new therapeutics that are less toxic and have fewer side effects, promote better adherence, and are readily accessible, particularly in resource-limited settings (http://www3.niaid.nih.gov/research/topics/HIV/therapeutics/intro/default.htm).

Specifically, with the support of NIAID, therapeutic agents have been developed to treat the diseases caused by HIV and its co-infections and to prevent maternal-child transmission of HIV. Therapeutic agents can be small molecules, such as nucleosides, or large biopharmaceutical agents, such as antibodies or therapeutic vaccines. The U.S. Food and Drug Administration (FDA) maintains a current listing of HIV/AIDS therapeutics (http://www.fda.gov/oashi/aids/status.html) that have been approved by that agency.

NIAID’s research agenda for developing HIV/AIDS therapeutics is guided by the NIH Office of AIDS Research (OAR), the entity responsible for the overall scientific, budgetary, legislative, and policy elements of all AIDS research sponsored by NIH. NIAID has long played a central role in pursuing the following research goals:

- **Drug Discovery**—to identify and validate new targets critical to the replication of HIV and its co-infections, and to evaluate new therapeutic agents and strategies for potential activity in cell culture and in animal efficacy models.
- **Preclinical Drug Development**—to conduct translational activities (bulk drug synthesis, analytical chemistry, formulation development, animal pharmacology and toxicology) to convert promising lead compounds into pharmaceutical agents suitable for clinical evaluation.
- **Clinical Research**—(i) to conduct clinical research on new therapies and treatment regimens for treating HIV and its co-infections; (ii) to evaluate approaches to prevent the transmission of HIV, improve and sustain an HIV-individual’s immune function, overcome drug resistance, and eradicate HIV from latent tissue reservoirs; and (iii) to investigate the metabolic changes and complications associated with the use of highly active antiretroviral therapy.

### 30.1 Drug Discovery

#### 30.1.1 HIV Targets

The identification of viral and cellular drug targets relevant to the human immunodeficiency virus is essential for fueling the drug development pipeline (http://www3.niaid.nih.gov/research/topics/HIV/therapeutics/intro/drug_discovery.htm).

Early drug discovery efforts concentrated on a relatively small number of viral targets: HIV reverse transcriptase (an enzyme that catalyzes the synthesis of viral DNA within infected cells from the RNA template carried by infectious virions) and HIV protease (an enzyme that cleaves and processes viral precursor proteins that allow the virion to mature). Treatment regimens containing combinations of reverse transcriptase and protease inhibitors, commonly known as highly active antiretroviral therapy (HAART), revolutionized the treatment of people with HIV by markedly lowering viral load and decreasing the incidence of AIDS-associated opportunistic infections. Many patients receiving HAART nevertheless suffer metabolic abnormalities and drug toxicities, have difficulty adhering to the complex drug regimens, and develop strains of HIV resistant to therapy.

Additional viral and cellular targets are now being extensively studied, and therapies targeting HIV integrase, various steps of the virus entry process, and virion maturation have been examined in clinical trials (e.g., Phase II/III) in recent years. Still in the early stages of preclinical investigation are potential inhibitors of Vif/APOBEC; ESCRT I, II, and III (virus assembly); and TRIM5α (virus uncoating) (http://www3.niaid.nih.gov/topics/HIVAIDS/Research/BasicScience/targinter.htm).
30.1.2 Co-infections

HIV-infected individuals without access to effective treatment regimens to combat their HIV infection commonly manifest diseases caused by co-infection with infectious agents, such as Mycobacterium avium, Pneumocystis jirovecii, Cryptosporidium parvum, cryptococci, fungi, and human cytomegalovirus, as well as other HIV/AIDS-associated conditions, such as neuropathy, wasting, and various malignancies.

Diseases caused by opportunistic pathogens are less common nowadays in AIDS patients receiving HAART; however, the incidence of co-infection with hepatitis C virus (HCV) or tuberculosis (TB) has increased, especially in countries where the risk of co-infection is high.

As a result of prolonged survival, greater numbers of HIV-infected individuals are exhibiting long-term complications of HCV infection, namely end-stage liver disease and hepatocellular carcinoma. Infection by HCV in some instances has been shown to interfere with HAART regimens. TB can accelerate the progress of AIDS and is currently the leading cause of death in persons who are HIV-positive.

30.2 Preclinical Drug Development

Any new therapeutic agent with demonstrated activity in cell culture and in animal efficacy models requires many additional studies to convert it from a promising lead into a pharmaceutical agent suitable for evaluation in clinical trials (http://www3.niaid.nih.gov/research/topics/HIV/therapeutics/intro/preclinical_drug_dev.htm). These product development (or “translational”) activities are designed to generate the necessary pharmaceutical-grade materials and preclinical data needed to support the submission of an Investigational New Drug (IND) application to the FDA. The types of preclinical studies required include scale-up synthesis of the therapeutic agent, development of analytical assays to detect and quantitate the therapeutic agent and its metabolites, development and manufacture of dosage formulations, and animal pharmacology and toxicology. Many of these studies require compliance with current FDA regulations regarding Good Manufacturing Practices and Good Laboratory Practices.

30.3 Clinical Research

Once a new therapeutic agent or strategy has been thoroughly studied in preclinical studies, the information generated typically is submitted to the FDA as part of an IND application. Evaluation of the therapeutic agent or strategy in human subjects can commence once FDA has approved the IND application.

Clinical trials commonly are designed to investigate the safety and effectiveness of new therapeutic agents for treating HIV and its co-infections. Studies also are conducted to evaluate strategies for the best use of these therapeutic agents in combination with other agents, including ways of minimizing drug-related complications. With the advent of HAART, the complications associated with HIV infection have expanded to include changes in metabolism and morphologic complications caused both by HIV disease and the use of antiretroviral agents. These metabolic changes include altered body fat distribution or lipodystrophy, insulin resistance, elevated triglyceride and cholesterol levels, bone demineralization, and elevated lactate levels. The underlying pathogenic mechanisms of these changes and association with immune activation are unknown or poorly understood, and the long-term consequences, including increased risk of cardiovascular disease, are under investigation (http://www3.niaid.nih.gov/research/topics/HIV/therapeutics/intro/clin_research.htm).

30.3.1 Clinical Trial Units and HIV/AIDS Networks

NIAID is currently supporting the world’s largest HIV/AIDS clinical research effort. In a newly restructured system of six HIV/AIDS clinical research networks, NIAID has selected 60 U.S. and international institutions as HIV/AIDS Clinical Trials Units (CTUs)—the total number of CTUs is expected to reach 73 (http://www3.niaid.nih.gov/news/newsreleases/2007/ctu07.htm). These Clinical Trials Units are intended to carry out the next generation of HIV/AIDS research on vaccines, prevention, and treatment, and to work with the NIAID clinical research networks in a flexible, collaborative, and coordinated way to tackle the critical research questions that can help accelerate progress against the HIV/AIDS pandemic.

The CTU initiative represents the second step of a two-part restructuring process of NIAID’s HIV/AIDS clinical trials networks. NIAID announced the clinical investigators and institutions responsible for leading the new networks in June 2006 (http://www3.niaid.nih.gov/news/newsreleases/2006/leadership.htm). Each CTU is a member of one or more of the six NIAID HIV/AIDS networks: the AIDS Clinical Trials Group, the HIV Prevention Trials Network, the HIV Vaccine Trials Network, the International Maternal Pediatric Adolescent AIDS Clinical Trials