AREA OF FOCUS #5

AIDS

The human immunodeficiency virus (HIV) infection leading to acquired immunodeficiency syndrome (AIDS) is a relatively recent epidemic and an important public health problem both in the United States and across the globe.

The four distinct groups of individuals in whom the epidemic is rapidly spreading are male homosexuals, injecting drug users, infants of untreated or undetected HIV-positive women, and heterosexual persons, principally in minority communities where HIV infection is facilitated by high rates of other sexually transmitted diseases.

More than 600,000 persons have been diagnosed with AIDS in the United States. A larger number are infected with HIV, many of whom are not yet diagnosed. In the United States, African-Americans and Hispanic or Latino Americans are disproportionately infected with HIV.

Persons infected with HIV may develop a multisystem dysfunction, and those with AIDS typically have severe abnormalities in many organ systems.

Persons infected with HIV with or without AIDS may develop severe metabolic abnormalities, including severe wasting syndrome.

Individuals coinfected with hepatitis C may follow a more virulent course to severe morbidity and/or death.

Development of HIV-related nephropathy may occur early in the course of the disease, with or without AIDS, and may progress to end-stage renal disease. Between 1993 and 1997, AIDS nephropathy was the reported cause of ESRD in 1 percent of all incident ESRD patients but was the fourth leading cause of ESRD in African-Americans.

Current Activities

Liver and Pancreatic Disease in HIV Infection

Background

The current initiative specifically targets hepatic and pancreatic comorbidities in the context of HIV infection and the metabolic complications of antiretroviral treatment in support of basic and clinical research that addresses the significant emerging clinical issues of disease progression in patients with HIV infection.

Highly active antiretroviral therapy (HAART) has slowed the progression of HIV disease and decreased the rate of HIV-associated mortality. In the context of enhanced longevity for HIV patients, other comorbidities, such as chronic liver disease and pancreatitis, can assume greater importance in the medical management of patients. Based on shared routes of transmission, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are common in HIV-infected patients. HIV infection has a significant effect on the natural history of HBV infection, with coinfected individuals more likely to experience severe liver disease. Individuals treated with lamivudine as part of their antiretroviral treatment more frequently fail treatment, resulting in the emergence of drug-resistant strains of HBV. Several studies have also documented that HIV modifies the natural history of chronic HCV infection, leading to an accelerated course of progression to end-stage liver disease and death. It has been suggested that the accelerated course to end-stage liver disease could be reduced from the two- to four-decade timeframe for HCV monoinfection to as little as 5 to 6 years in HCV/HIV-coinfected patients. The result of the common occurrence of hepatitis and HIV coinfection and accelerated disease progression is the report that end-stage liver disease is now the leading cause of death in hospitalized HIV-infected patients.

The etiology and pathogenesis of enhanced progression to end-stage liver disease in HIV-coinfected patients is unknown. Recent data have shown that hepatitis coinfection results in enhanced liver disease in individuals infected with HIV through enhanced severity of fibrosis, a higher frequency of cirrhosis and end-stage liver disease, as well as increased deaths due to liver disease. The role of HCV quasispecies, the effects of immune deficiency on the course of hepatitis C, hepatotoxicity due to antiretroviral treatment, chronic HBV infection, immune restoration and HBV infection, and the development of nonalcoholic steatohepatitis (NASH) as a result of lipodystrophy have all been hypothesized to play a role in the enhanced liver disease seen in coinfected individuals. Additional research is needed to identify the mechanism(s) of pathogenesis and to identify therapeutic targets for treatment.

This Program Announcement (PA) invites clinical and basic research applications that focus on the pathogenesis and therapeutics of liver and pancreatic disease associated with coinfections that occur in patients with HIV infection or the metabolic complications associated with the treatment of HIV infection. The coinfections targeted by this PA specifically include hepatitis B and hepatitis C, which are frequent causes of end-stage liver disease, a leading

cause of death in HIV-infected patients. Metabolic complications that involve the liver and pancreas and that are associated with the treatment of HIV infection include hepatic drug toxicity, hepatic lipid metabolism, NASH, and pancreatitis, which are all important causes of morbidity in patients with HIV infection. The proposed studies should advance our understanding of the pathogenesis of liver and pancreatic disease in patients with HIV and/or metabolic complications of therapy. These advances should lead to enhanced medical management of individuals infected with HIV.

Research Goals and Scope

This initiative will support basic and clinical research in HIV coinfection and metabolic disease related to antiretroviral treatment. Areas of interest include, but are not limited to, the following:

- The elucidation of a biological mechanism(s) that promotes enhanced progression of liver disease in HIV-infected patients
- A further elucidation of drug-induced hepatotoxicity associated with antiretroviral treatment regimens
- The identification of therapeutic targets and/or novel therapies for the treatment of liver disease in HIV-infected patients
- The elucidation of synergy between HIV and HCV, resulting in enhanced liver disease
- The enhanced knowledge of antiviral treatment failures of HBV/HIV coinfection and the emergence of HBV drug-resistant strains
- The identification of an underlying liver disease, such as NASH, in combination with HIV infection and antiretroviral treatment that progresses to end-stage liver disease
- Therapeutics development for the enhanced medical management of patients with HBV/HIV or HCV/HIV coinfection or the metabolic abnormalities due to antiretroviral treatment
- Altered hepatic lipid metabolism due to antiretroviral treatment
- HIV-associated pancreatitis and risk factors, including hypertriglyceridemia, obesity, and gallstones
- The impact of liver transplantation on disease progression in select patients with coinfection with hepatitis B or hepatitis C.

Performance Measures

The performance measures will include the total number of grants awarded, the number of patients successfully recruited, and the funding level.

Outcome Measure

The outcome measure will be the extent to which the results alter clinical practice, including the diagnosis, prevention, and management of HIV patients with liver and pancreatic disease.

Treatment of HAART-Associated Metabolic Changes in Patients With HIV Infection

Background

In recent years, the advent of highly active antiretroviral therapy has dramatically improved the survival of patients with HIV infection. Despite the clear benefits of the new antiretroviral therapies, HAART has been associated with a variety of metabolic complications—including dyslipidemia, insulin resistance, and abnormal distribution of body fat (lipodystrophy). These metabolic abnormalities represent major risk factors for the development of other serious diseases, such as diabetes and CVD. More recently, reports of clinically significant osteopenia have been emerging in HAART-treated patients.

Lipodystrophy, characterized by increased deposition of fat (lipohypertrophy) in the abdomen and trunk and/or loss of fat (lipoatrophy) in the face and extremities, appears to occur commonly in patients on HAART. Currently, it is not clear whether abdominal lipohypertrophy is simply accompanied by peripheral lipoatrophy or whether these changes constitute two separate entities. The lipodystrophic changes have been a particular issue for many affected individuals. In addition to concerns over the potential long-term health implications of these body composition changes, distress over these often disfiguring changes has caused some patients to stop taking antiretroviral medications.

HAART has also been increasingly associated with hyperinsulinemia and impaired glucose tolerance; to date, frank diabetes has been reported less frequently. However, concern about the eventual progression to diabetes is real, particularly in those patients who also have accumulation of abdominal (particularly visceral) fat.

Patients receiving HAART frequently develop hypertriglyceridemia, which can be extreme, as well as hypercholesterolemia. Elevated total and LDL cholesterol levels, which occur following the institution of HAART, may be superimposed on low HDL cholesterol levels, which have been described in HIV-infected patients prior to initiating any therapy. In non-HIV-infected individuals, the coexistence of dyslipidemia and insulin resistance or diabetes confers additive risk for the development of atherosclerotic heart disease, making these HAART-associated side effects a serious potential public health concern.

Large epidemiological studies are currently ongoing to better describe the metabolic changes associated with HAART and to understand whether particular drugs, or classes of drugs, are the etiologic agents of these changes. In addition, a large research effort is aimed at understanding the molecular mechanism(s) by which antiretroviral drugs might lead to these metabolic abnormalities. A long-term goal of such research might be the development of new, highly active anti-HIV drugs that lack these adverse metabolic consequences.

In the meantime, it is essential to develop strategies to normalize lipid levels, insulin sensitivity, and body fat distribution and to minimize bone loss to enhance patient compliance and to decrease the risk for future disease. The safety and efficacy of lipid-lowering drugs or diabetes medications have not been extensively studied in patients infected with HIV and/or receiving HAART. It is not known whether adverse drug interactions might affect efficacy and safety or whether the underlying infection with HIV (or other opportunistic infections) might affect treatment success. For example, the metabolism and clearance of some statins may be affected by concomitant use of protease inhibitors. Some available drugs (e.g., metformin, thiazolidinediones) will be contraindicated because of coexisting renal or liver disease in patients with AIDS. In addition, attention must be paid to other risk factors for diabetes and CVD, such as smoking, physical inactivity, diet, and hypertension.

A Request for Applications (RFA) will be issued in collaboration with the National Heart, Lung, and Blood Institute to encourage applications to develop and test strategies for treating the metabolic complications associated with antiretroviral drug therapy in patients with HIV infection.

Research Goals and Scope

This RFA solicits clinical studies to (1) test the efficacy, in patients infected with HIV, of agents currently approved for the treatment of dyslipidemia, insulin resistance or diabetes, and osteoporosis/osteopenia and (2) develop and test novel treatment approaches to the metabolic consequences of anti-HIV therapy, including lipodystrophy.

Appropriate topics for investigation under this RFA would include the following:

- Studies to examine the effects of currently available pharmacotherapies for the treatment of insulin resistance or diabetes, hypercholesterolemia and/or hypertriglyceridemia, and osteoporosis or osteopenia in the metabolic syndromes associated with HAART
- Studies to identify potential drug interactions between HAART and current pharmacotherapies for the treatment of insulin resistance or diabetes, hypercholesterolemia and/or hypertriglyceridemia, and osteoporosis or osteopenia
- Studies to identify and test new therapies to prevent or reverse the metabolic complications associated with HAART
- Studies to evaluate the efficacy of diet and exercise alone, or in combination with medication, in reversing dyslipidemia and insulin resistance or diabetes in patients on HAART
- Studies to evaluate whether switching anti-HIV drugs is an effective approach to the treatment of metabolic changes
- Studies to test agents that affect fat deposition and/or metabolism for the treatment of HAART-associated lipodystrophy

Performance Measures

The performance measures will include the number of grants awarded, the quality of proposals, and the level of funding.

Outcome Measure

The outcome measure will be the successful improvement in clinical practice, including treatment approaches to the metabolic consequences of anti-HIV therapy.

Semen in Transmission of HIV

Background

HIV in semen is one the major factors in the development of the AIDS epidemic. Sexual contact with HIV-seropositive men is a major route for transmission of HIV. Sources of HIV transmission in semen have been identified as both the free virus particles and infected cells. Confounding factors in the study of the biology of HIV in semen are the limited knowledge of the relationship among systemic host factors, the levels of potentially infectious HIV in the semen, and the immunology of the male urogenital tract. The anatomical origins and sources of HIV in the male urogenital tract have not been positively identified, neither have the effects of therapeutic interventions on HIV infectivity. This initiative is the outcome of a planning meeting convened in spring 2000 to review the state of knowledge and to develop a research plan.

Research Goals and Scope

The purpose of this initiative is to develop studies that will elucidate factors determining HIV transmission and shedding in the male urogenital tract. Other important research areas include the elucidation of HIV infectivity in semen fractions; the relationship between the immunobiology of the male urogenital tract and HIV replication and infectivity; and factors that influence HIV transmission through semen, such as urogenital tract inflammation.

Performance Measures

The performance measures will include the number of grants, the quality of the proposals, and the level of funding.

Outcome Measure

The outcome measure will be the use of the results in altering clinical practice, including preventing the transmission of HIV.