

FOIA MARKER

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Stack:	Row:	Section:	Shelf:	Position:
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Mixing AMTR of the IDEAL
Characteristics;

ideally
What this model would achieve

Pro Yield clinical
~~Produce~~ answers we don't have now and are not likely to be able to do through separate Federal and private efforts. *Improve the clinical care for persons living HIV.*

~~Provide insurers with information to assist them in decision-making efforts.~~

Patients will know they can go on trials without fear of losing health care benefits.

What studies

can valid
■ ~~Support~~ scientific studies that would provide useful clinical care information useful patients and their clinicians. clinical

■ Support studies that would provide useful cost-effectiveness information to private insurers, Medicare, Medicaid, ADAP programs, HRSA-sponsored programs, CHCs, etc.

■ Ensure that studies are well-designed and will answer the questions asked.

Complement the government-sponsored trials.

Look at studies governemtn and the pharmaceutical industry is not likely to sponsor in great numbers, i.e. alternative and complementary therapies.

How

■ Fair arbitration of what types of scientific questions to ask, i.e. all interested groups would have a say about what questions would be useful (insurers, patients and their advocates, government (NIH, FDA), etc.), researchers, pharmaceutical companies, etc.

Possible mechanism would be a public/private partnership.

bring
This groups could ~~focus~~ expertise that government or industry may need -- i.e. design of large simple trials.

■ Studies would be conducted under the highest scientific and ethical standards, i.e. appropriate patient protections, informed consents, appropriate interim monitoring of studies for safety and effectiveness, etc.

■ Provide participating clinicians with easy access to available trials.

Patients

Outcomes

■ Information would be disseminated to all participants. Data could be used ~~by government~~ in developing standard of care guidelines, by researchers, industry, and the public/private partnership in developing future studies.

Government -- good research to use for making improvements in clinical care for persons with HIV

(A) Insurer (CHAMPUS)

The health insurance program provided by the DOD.

CHAMPUS would provide basic health care and serve as an access point for entry to the NCI-sponsored clinical trials.

(B) Federal Government

The DOD, through CHAMPUS, will provide reimbursement for medical care required as a result of participation in NCI-approved clinical trials. This includes purchasing and administering all approved chemotherapy agents (investigational agents are provided by the pharmaceutical sponsor), inpatient and outpatient care, including diagnostic and laboratory services not otherwise reimbursed under an NCI grant program.

The NCI provides research protocols and will review for scientific merit, duplication of existing studies, patient safety, and adequacy of regulatory and human subject protection aspects. NCI will cover any research-specific costs (e.g., additional lab tests, additional hospital days than might have been needed for conventional treatment, etc.).

(C) Pharmaceutical Companies

Would provide the therapeutic agent under study.

(D) Patients

Would have access to clinical trials and the expert care provided in the research setting.

(E) Academic Health System

Patients could be referred to academic health centers participating in conduct of the NCI-sponsored trials.

(2) Advantages

Progress in cancer research, because more of the large scale efficacy studies that are needed to assess the relative effectiveness of treatments can be completed;

Increases patients' access to innovative therapies;

Patients can enter into trials without fear of losing health benefits. (In the past, CHAMPUS regulations have barred reimbursements for medical care delivered as part of a research study.);

Possible avoidance of lawsuits by CHAMPUS due to the denial of benefits associated with trials;

CHAMPUS will have guarantee that the NCI-sponsored trials will be scientifically valid and produce sound results;

Pharmaceutical companies can have access to a clinical trials infrastructure for testing their drugs;

The Federal government will have the ability to analyze the cost and economic impact of integrating a health delivery system with a federally-supported clinical research infrastructure. This data can be used by Federal health service programs (Medicare and Medicaid) and private insurers.

A v. B
CWC

RESEARCH

Agency: National Institutes of Health

Goal: Develop and evaluate vaccines for prevention of HIV transmission and infection.

Objective 1: Enhance understanding about host defense mechanisms and protection against HIV infection and disease.

Action Steps: Support research on protective immune responses.

~~Conduct and support research to develop vaccines for prevention of HIV transmission and infection~~

Objective: Vaccines

~~Action Steps: Increase scientific knowledge about host defense mechanisms and protection against HIV infection and disease~~

Descriptions: Develop nonhuman primate and other animal models for HIV vaccine evaluation; determine immune responses that affect infection and disease course; focus on chronic infection with attenuated virus versus wild-type virus; determine why disease does not occur or is delayed in some models;

Determine the correlates of immune protection against, and immunologically mediated control of HIV; ~~and immunologically mediated control of, HIV;~~

Study acutely infected individuals, exposed/uninfected humans (and other primates), and rapid/nonprogressors to determine viral and host factors that impact clearance of circulating virus and disease course; ensure that plasma, PBMC, biopsy, autopsy, and other key patient and animal samples, including CNS samples, are accessible to qualified laboratories;

Elucidate the three-dimensional structure of viral epitopes and determine the mechanism of escape from antibody-mediated neutralization and recognition by cytotoxic T cells; — Elucidate
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Define conserved viral epitopes that are potentially relevant to protective immune responses; devise strategies to enhance their immunogenicity;

Determine the molecular nature of HIV genetic and antigenic

diversity and incorporate the findings into ongoing vaccine development; focus on characterization of HIV at potential efficacy trial sites;

Foster multidisciplinary approaches that bridge basic, animal, and clinical approaches; and

Develop quantitative measures of HIV concentration in bodily fluids to determine whether there is a relationship between HIV concentration and transmission.

Objective 2: Identify strategies for eliciting protective immune responses.

~~FY 95: 45,~~

Action Steps: Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models.
~~and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models~~

Descriptions: Develop further multidisciplinary approaches for the design and development of potential vaccine candidates; ~~expand research on mucosal delivery and stimulation of mucosal immune responses; expand research on mucosal delivery and stimulation of mucosal immune responses (NIAID);~~

Include research on but not limited to: whole-particle designs such as whole-killed HIV and genetically engineered,

~~whole-particle designs such as whole-killed HIV and genetically engineered,~~ noninfectious HIV mutants that lack the viral RNA genome or have a defect in a critical protein but contain a full complement of HIV antigenic proteins; live,

live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins; genetically engineered,

genetically engineered, live-attenuated strains of HIV; synthetic peptide candidates capable of inducing and boosting both cellular and humoral immunity; DNA candidates as HIV vaccines; combination strategies including priming and boosting;

Evaluate vaccine strategies in AIDS animal models;

~~synthetic peptide candidates capable of inducing and boosting both cellular and humoral immunity;~~

~~DNA candidates as HIV vaccines;~~

~~combination strategies including priming and boosting;~~

~~Evaluate vaccine strategies in AIDS animal models:~~

~~place additional emphasis on strategies in or about to be in clinical trial, practical immunization schedules, and challenge routes and viral isolates that most closely mimic the human experience;~~

~~delineate the mechanisms of immune protection; conduct transfer experiments to help dissect immune correlates;~~

~~determine the impact of dose on the nature and effectiveness of the immune response;~~

~~examine protection from organ specific as well as systemic infection;~~

~~conduct long term followup of vaccinated animals that become chronically infected to determine the impact of vaccination on disease progression;~~

Encourage development of candidate vaccines suitable for domestic and international use;

Conduct research on adjuvants and novel formulations that have a qualitative or quantitative impact on immunologic responses to vaccine candidates;

Evaluate strategies to decrease or eliminate HIV from sexual fluids; Characterize and evaluate the potential negative side effects of candidate vaccines,

~~Characterize and evaluate the potential negative side effects of candidate vaccines, including production of enhancing antibodies and neurotoxicity; and~~

Develop methodologies for comparative *in vitro* measure of immune function.

Objective 3: Evaluate efficacy of vaccine candidates.

FY 95: 24,135

FY 96: 25,465

Populations Served: All populations

Constituency Involvement:—

Unmet Need:—

Objective: Vaccines

Action Steps: Identify appropriate domestic and international populations and develop infrastructure, and develop behavioral research and community education and outreach activities, that are necessary for ensuring adequate performance of Phase III efficacy clinical trials.
~~including behavioral research and community education and outreach activities, that is necessary for ensuring adequate performance of Phase III efficacy clinical trials~~

Descriptions: Prepare for adequate followup of individuals participating in vaccine clinical trials to determine the longevity of immune response, the correlates of immune protection, long-term safety, the impact of participation on risk-taking behavior, and the possible positive or negative effects of vaccine immunization against disease progression and HIV transmission;

Utilize infrastructures established for the conduct of AIDS vaccine efficacy trials to implement prevention research activities designed to determine the efficacy of other biomedical or behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the population; evaluate promising interventions separately and/or as a component of prophylactic vaccine efficacy trials;

Continue appropriate epidemiologic studies that determine the risk profiles and infection rates of various populations in the United States and internationally in order to identify those groups most likely to be the participants in vaccine trials;

Maintain and expand the AIDS Vaccine Clinical Trials Network to include domestic and international sites with access to populations at high risk for acquiring HIV infection and where vaccine or other prevention research activities may be feasible;

Maintain the necessary laboratory and epidemiologic research infrastructure at designated sites for conducting domestic and international vaccine efficacy trials; develop optimal assays to distinguish infection from seroconversion to the vaccine;

Acquire and analyze HIV isolates from recent seroconverters representative of potential efficacy trial populations so that genetic and antigenic information about virus circulating in the population can be obtained;

Conduct behavioral research in populations at high risk for HIV infection, particularly those difficult-to-reach populations that have been historically underrepresented in

clinical trials; determine optimal education, risk-reduction intervention, recruitment, adherence, and retention approaches and estimate behavior changes and other factors pertinent to the design and execution of a successful efficacy trial;

Establish linkages with communities or community organizations where efficacy trials might be conducted to optimize education, recruitment, and followup activities and to help address community concerns related to AIDS vaccine efficacy trials;

Link infrastructure development and vaccine research activities in high-risk populations with other prevention and treatment research activities in these populations, including research on TB and STDs;

Conduct research to determine optimal methods of achieving truly informed consent; and

Conduct research to determine possible adverse social, economic, or legal consequences of participation in clinical trials and develop strategies to mitigate potential harm.

Objective 4: Develop a preventive vaccine for newborns and infants.

Action Steps: Identify mechanisms of protective immunity to HIV in newborns and infants and develop a safe and effective immunologic strategy to prevent HIV infection in this population.

~~FY 95: 19,189~~

~~FY 96: 19,912~~

~~Populations Served: All populations~~

~~Constituency Involvement:~~

~~Unmet Need:~~

~~Objective: Vaccines~~

~~Action Steps:~~ Identify mechanisms of protective immunity to HIV in newborns and infants and develop a safe and effective immunologic strategy to prevent HIV infection in this population

Descriptions: Evaluate genetic and antigenic variation in viruses transmitted from mothers to infants and in maternal isolates that are not transmitted;

Accelerate studies of maternal-infant transmission;

Develop and maintain domestic and international infrastructure necessary to enroll mothers and infants in prospective long-term followup vaccine trials;

Determine the immunogenicity of various vaccines and adjuvants in newborns and infants;

Determine which maternal and infant immune responses are associated with nontransmission of HIV;

Identify antibody preparations for use as passive or passive/active HIV prevention;

Establish criteria for advancement of candidates in Phase I, Phase II, and Phase III clinical trials; and

Conduct Phase I, Phase II, and Phase III clinical trials of the most promising candidates that meet established criteria.

Objective 5: Identify promising vaccine candidates for efficacy trials.

~~FY 95:~~ 3,174

~~FY 96:~~ 3,501

~~Populations Served:~~ All populations

~~Constituency Involvement:~~

~~Unmet Need:~~

~~Objective: Vaccines~~

Action Steps: Develop criteria for selection of suitable candidate vaccines, support appropriate infrastructure, and ~~conduct Phase I and Phase II trials.~~
~~and conduct Phase I and Phase II trials~~

Descriptions: Utilize vaccine selection committees to carefully evaluate promising candidates; emphasize need for thorough consideration of efficacy in animal models;

Conduct Phase I and Phase II clinical trials that will determine safety and delineate comparative immunologic analysis of candidates for preventive vaccines; expand immunologic measurements to include a broad range of cell-mediated and mucosal immune responses;

Conduct Phase II trials in high-risk individuals of the most promising preventive vaccine candidates or combinations that proved promising in Phase I trials conducted in low-risk individuals and that have genetic or immunologic relatedness to HIV isolates circulating in the proposed trial population;

Support and maintain the AIDS Vaccine Evaluation Groups;

Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with research on therapeutic AIDS vaccines, e.g., the use of candidate vaccines to ameliorate disease when administration is initiated after establishment of chronic infection;

Acquire and analyze HIV isolates from recent seroconverters representative of Phase I and Phase II trial populations so that genetic and antigenic information about viruses circulating in the population can be obtained; and

Conduct behavioral research pertinent to preparation for Phase III trials.

~~Objective 6: Conduct vaccine efficacy studies.~~

Action Steps: Establish criteria for selection of suitable vaccine candidates and conduct Phase III clinical trials when established criteria are met.

~~FY 95: 19,398~~

~~FY 96: 21,177~~

~~Populations Served:~~ All populations

~~Constituency Involvement:~~

~~Unmet Need:~~

Objective: Vaccines

~~**Action Steps:** Establish criteria for selection of suitable vaccine candidates and conduct Phase III clinical trials when established criteria are met~~

Descriptions: Establish criteria with concurrence of an advisory group that has the requisite scientific, public health, government, and community expertise;

Conduct large-scale efficacy trials of novel preventive vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet established criteria;

Evaluate HIV vaccine candidate efficacy;

Evaluate multiple scientific hypotheses; and

Ensure that trials are conducted with the highest regard for social and ethical concerns of the participants.

FY 95: 111, 200

~~**FY 96:** 229~~

~~**Populations Served:** All populations~~

~~**Constituent Involvement:**~~

~~**Unmet Need:**~~

~~THE FOLLOWING TEXT WAS MOVED~~

~~831~~

~~**FY 96:** 118, 128~~

Pops. Served: All populations

Constituency Involvement: Researchers, clinicians, community and patient representatives, NIAID Advisory Council, ARAC, and OAR Advisory Committees. Others?

Unmet Needs: The NIH FY 1996 Plan and Budget Estimate for Scientific Opportunities in HIV-Related Research identified areas for further productive research in this area in the amount of \$36,643 over the FY 96 figure. 47,844

~~**Populations Served:** All populations~~

~~**Constituency Involvement:**~~

~~**Unmet Need:**~~

~~Objective: Vaccines~~

~~THE PRECEDING TEXT WAS MOVED~~

Strategy version

RESEARCH

Agency: National Institutes of Health

Goal: Develop and evaluate vaccines for prevention of HIV transmission and infection.

Objective 1: Enhance understanding about host defense mechanisms and protection against HIV infection and disease.

Action Steps: Support research on protective immune responses.

Descriptions: Develop nonhuman primate and other animal models for HIV vaccine evaluation; determine immune responses that affect infection and disease course; focus on chronic infection with attenuated virus versus wild-type virus; determine why disease does not occur or is delayed in some models;

Determine the correlates of immune protection against, and immunologically mediated control of HIV;

Study acutely infected individuals, exposed/uninfected humans (and other primates), and rapid/nonprogressors to determine viral and host factors that impact clearance of circulating virus and disease course; ensure that plasma, PBMC, biopsy, autopsy, and other key patient and animal samples, including CNS samples, are accessible to qualified laboratories;

Elucidate the three-dimensional structure of viral epitopes and determine the mechanism of escape from antibody-mediated neutralization and recognition by cytotoxic T cells;

Define conserved viral epitopes that are potentially relevant to protective immune responses; devise strategies to enhance their immunogenicity;

Determine the molecular nature of HIV genetic and antigenic diversity and incorporate the findings into ongoing vaccine development; focus on characterization of HIV at potential efficacy trial sites;

Foster multidisciplinary approaches that bridge basic, animal, and clinical approaches; and

Develop quantitative measures of HIV concentration in bodily fluids to determine whether there is a relationship between HIV concentration and transmission.

Objective 2: Identify strategies for eliciting protective immune responses.

Action Steps: Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models.

Descriptions: Develop further multidisciplinary approaches for the design and development of potential vaccine candidates; expand research on mucosal delivery and stimulation of mucosal immune responses;

Include research on but not limited to: whole-particle designs such as whole-killed HIV and genetically engineered, noninfectious HIV mutants that lack the viral RNA genome or have a defect in a critical protein but contain a full complement of HIV antigenic proteins; live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins; genetically engineered, live-attenuated strains of HIV; synthetic peptide candidates capable of inducing and boosting both cellular and humoral immunity; DNA candidates as HIV vaccines; combination strategies including priming and boosting;

Evaluate vaccine strategies in AIDS animal models;

Encourage development of candidate vaccines suitable for domestic and international use;

Conduct research on adjuvants and novel formulations that have a qualitative or quantitative impact on immunologic responses to vaccine candidates;

Evaluate strategies to decrease or eliminate HIV from sexual fluids; ~~Characterize and evaluate the potential negative side effects of candidate vaccines, including production of enhancing antibodies and neurotoxicity; and~~

Develop methodologies for comparative *in vitro* measure of immune function.

Objective 3: Evaluate efficacy of vaccine candidates.

Action Steps: Identify appropriate domestic and international populations and develop infrastructure, and develop behavioral research and community education and outreach activities, that are necessary for ensuring adequate performance of Phase III efficacy clinical trials.

Descriptions: Prepare for adequate followup of individuals participating in vaccine clinical trials to determine the longevity of immune response, the correlates of immune protection, long-term safety, the impact of participation on risk-taking behavior, and the possible positive or negative effects of vaccine immunization against disease progression and HIV transmission;

Utilize infrastructure established for the conduct of AIDS vaccine efficacy trials to implement prevention research activities designed to determine the efficacy of other biomedical or behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the population; evaluate promising interventions separately and/or as a component of prophylactic vaccine efficacy trials;

Continue appropriate epidemiologic studies that determine the risk profiles and infection rates of various populations in the United States and internationally in order to identify those groups most likely to be the participants in vaccine trials;

Maintain and expand the AIDS Vaccine Clinical Trials Network to include domestic and international sites with access to populations at high risk for acquiring HIV infection and where vaccine or other prevention research activities may be feasible;

Maintain the necessary laboratory and epidemiologic research infrastructure at designated sites for conducting domestic and international vaccine efficacy trials; develop optimal assays to distinguish infection from seroconversion to the vaccine;

Acquire and analyze HIV isolates from recent seroconverters representative of potential efficacy trial populations so that genetic and antigenic information about virus circulating in the population can be obtained;

Conduct behavioral research in populations at high risk for HIV infection, particularly those difficult-to-reach populations that have been historically underrepresented in clinical trials; determine optimal education, risk-reduction intervention, recruitment, adherence, and retention approaches and estimate behavior changes and other factors pertinent to the design and execution of a successful efficacy trial;

Establish linkages with communities or community organizations where efficacy trials might be conducted to optimize education, recruitment, and followup activities and to help address community concerns related to AIDS vaccine efficacy trials;

Link infrastructure development and vaccine research activities in high-risk populations with other prevention and treatment research activities in these populations, including research on TB and STDs;

Conduct research to determine optimal methods of achieving truly informed consent; and

Conduct research to determine possible adverse social, economic, or legal consequences of participation in clinical trials and develop strategies to mitigate potential harm.

Objective 4: Develop a preventive vaccine for newborns and infants.

Action Steps: Identify mechanisms of protective immunity to HIV in newborns and infants and develop a safe and effective immunologic strategy to prevent HIV infection in this population.

Descriptions: Evaluate genetic and antigenic variation in viruses transmitted from mothers to infants and in maternal isolates that are not transmitted;

Accelerate studies of maternal-infant transmission;

Develop and maintain domestic and international infrastructure necessary to enroll mothers and infants in prospective long-term followup vaccine trials;

Determine the immunogenicity of various vaccines and adjuvants in newborns and infants;

Determine which maternal and infant immune responses are associated with nontransmission of HIV;

Identify antibody preparations for use as passive or passive/active HIV prevention;

Establish criteria for advancement of candidates in Phase I, Phase II, and Phase III clinical trials; and

Conduct Phase I, Phase II, and Phase III clinical trials of the most promising candidates that meet established criteria.

Objective 5: Identify promising vaccine candidates for efficacy trials.

Action Steps: Develop criteria for selection of suitable candidate vaccines, support appropriate infrastructure, and conduct Phase I and Phase II trials.

Descriptions: Utilize vaccine selection committees to carefully evaluate promising candidates; emphasize need for thorough consideration of efficacy in animal models;

Conduct Phase I and Phase II clinical trials that will determine safety and delineate comparative immunologic analysis of candidates for preventive vaccines; expand immunologic measurements to include a broad range of cell-mediated and mucosal immune responses;

Conduct Phase II trials in high-risk individuals of the most promising preventive vaccine candidates or combinations that proved promising in Phase I trials conducted in low-risk individuals and that have genetic or immunologic relatedness to HIV isolates circulating in the proposed trial population;

Support and maintain the AIDS Vaccine Evaluation Groups;

Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with research on therapeutic AIDS vaccines, e.g., the use of candidate vaccines to ameliorate disease when administration is initiated after establishment of chronic infection;

Acquire and analyze HIV isolates from recent seroconverters representative of Phase I and Phase II trial populations so that genetic and antigenic information about viruses circulating in the population can be obtained; and

Conduct behavioral research pertinent to preparation for Phase III trials.

Objective 6: Conduct vaccine efficacy studies.

Action Steps: Establish criteria for selection of suitable vaccine candidates and conduct Phase III clinical trials when established criteria are met.

Descriptions: Establish criteria with concurrence of an advisory group that has the requisite scientific, public health, government, and community expertise;

Conduct large-scale efficacy trials of novel preventive vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet established criteria;

Evaluate HIV vaccine candidate efficacy;

Evaluate multiple scientific hypotheses; and

Ensure that trials are conducted with the highest regard for social and ethical concerns of the participants.

FY 95: 111,831

FY 96: 118,128

Pops. Served: All populations

Constituency Involvement: Researchers, clinicians, community and patient representatives, NIAID Advisory Council, ARAC, and OAR Advisory Committees. Others?

Unmet Needs: The NIH FY 1996 Plan and Budget Estimate for Scientific Opportunities in HIV-Related Research identified areas for further productive research in this area in the amount of \$36,643 over the FY 96 figure.

Area Research

Goal 4 Conduct and support research to develop vaccines for prevention of HIV transmission and infection

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Vaccines	Increase scientific knowledge about host defense mechanisms and protection against HIV infection and disease	Develop nonhuman primate and other animal models for HIV vaccine evaluation; determine immune responses that affect infection and disease course; focus on chronic infection with attenuated virus versus wild-type virus; determine why disease does not occur or is delayed in some models; Determine the correlates of immune protection against, and immunologically mediated control of, HIV; Study acutely infected individuals, exposed/uninfected humans (and other primates), and rapid/nonprogressors to determine viral and host factors that impact clearance of circulating virus and disease course; ensure that plasma, PBMC, biopsy, autopsy, and other key patient and animal samples, including CNS samples, are accessible to qualified laboratories; Elucidate the three-dimensional structure of viral epitopes and determine the mechanism of escape from antibody-mediated neutralization and recognition by cytotoxic T cells. The identification of epitopes for which escape is not possible should receive more attention;	45,735	47,844	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (apprpr.)	FY 1996 (proposed)			
Vaccines	Increase scientific knowledge about host defense mechanisms and protection against HIV infection and disease (continued)	Define conserved viral epitopes that are potentially relevant to protective immune responses; devise strategies to enhance their immunogenicity; Determine the molecular nature of HIV genetic and antigenic diversity and incorporate the findings into ongoing vaccine development; focus on characterization of HIV at potential efficacy trial sites; Foster multidisciplinary approaches that bridge basic, animal, and clinical approaches; and Develop quantitative measures of HIV concentration in bodily fluids to determine whether there is a relationship between HIV concentration and transmission.					
Vaccines	Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models	Develop further multidisciplinary approaches for the design and development of potential vaccine candidates; expand research on mucosal delivery and stimulation of mucosal immune responses (NIAID);	24,135	25,465	All populations		
Vaccines	Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models (continued)	Include research on but not limited to: whole-particle designs such as whole-killed HIV and genetically engineered, noninfectious HIV mutants that lack the viral RNA genome or have a defect in a critical protein but contain a full complement of HIV antigenic proteins;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Vaccines	Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models (continued)	live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins; genetically engineered, live-attenuated strains of HIV; synthetic peptide candidates capable of inducing and boosting both cellular and humoral immunity; DNA candidates as HIV vaccines; combination strategies including priming and boosting;					
		Evaluate vaccine strategies in AIDS animal models: place additional emphasis on strategies in or about to be in clinical trial, practical immunization schedules, and challenge routes and viral isolates that most closely mimic the human experience; delineate the mechanisms of immune protection; conduct transfer experiments to help dissect immune correlates; determine the impact of dose on the nature and effectiveness of the immune response; examine protection from organ-specific as well as systemic infection;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Vaccines	Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models (continued)	conduct long-term followup of vaccinated animals that become chronically infected to determine the impact of vaccination on disease progression;					
		Encourage development of candidate vaccines suitable for domestic and international use;					
		Conduct research on adjuvants and novel formulations that have a qualitative or quantitative impact on immunologic responses to vaccine candidates;					
		Evaluate strategies to decrease or eliminate HIV from sexual fluids;					
		Characterize and evaluate the potential negative side effects of candidate vaccines, including production of enhancing antibodies and neurotoxicity; and					
Vaccines	Identify appropriate domestic and international populations and develop infrastructure, including behavioral research and community education and outreach activities, that is necessary for ensuring adequate performance of Phase III efficacy clinical trials	Develop methodologies for comparative <i>in vitro</i> measure of immune function.					
		Prepare for adequate followup of individuals participating in vaccine clinical trials to determine the longevity of immune response, the correlates of immune protection, long-term safety, the impact of participation on risk-taking behavior, and the possible positive or negative effects of vaccine immunization against disease progression and HIV transmission;	19,189	19,912	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Vaccines	Identify appropriate domestic and international populations and develop infrastructure, including behavioral research and community education and outreach activities, that is necessary for ensuring adequate performance of Phase III efficacy clinical trials (continued)	Utilize infrastructures established for the conduct of AIDS vaccine efficacy trials to implement prevention research activities designed to determine the efficacy of other biomedical or behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the population; evaluate promising interventions separately and/or as a component of prophylactic vaccine efficacy trials;					
		Continue appropriate epidemiologic studies that determine the risk profiles and infection rates of various populations in the United States and internationally in order to identify those groups most likely to be the participants in vaccine trials;					
		Maintain and expand the AIDS Vaccine Clinical Trials Network to include domestic and international sites with access to populations at high risk for acquiring HIV infection and where vaccine or other prevention research activities may be feasible;					
		Maintain the necessary laboratory and epidemiologic research infrastructure at designated sites for conducting domestic and international vaccine efficacy trials; develop optimal assays to distinguish infection from seroconversion to the vaccine;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Vaccines	Identify appropriate domestic and international populations and develop infrastructure, including behavioral research and community education and outreach activities, that is necessary for ensuring adequate performance of Phase III efficacy clinical trials (continued)	Acquire and analyze HIV isolates from recent seroconverters representative of potential efficacy trial populations so that genetic and antigenic information about virus circulating in the population can be obtained; Conduct behavioral research in populations at high risk for HIV infection, particularly those difficult-to-reach populations that have been historically underrepresented in clinical trials; determine optimal education, risk-reduction intervention, recruitment, adherence, and retention approaches and estimate behavior changes and other factors pertinent to the design and execution of a successful efficacy trial; Establish linkages with communities or community organizations where efficacy trials might be conducted to optimize education, recruitment, and followup activities and to help address community concerns related to AIDS vaccine efficacy trials; Link infrastructure development and vaccine research activities in high-risk populations with other prevention and treatment research activities in these populations, including research on TB and STDs;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Vaccines	Identify appropriate domestic and international populations and develop infrastructure, including behavioral research and community education and outreach activities, that is necessary for ensuring adequate performance of Phase III efficacy clinical trials (continued)	Conduct research to determine optimal methods of achieving truly informed consent; and Conduct research to determine possible adverse social, economic, or legal consequences of participation in clinical trials and develop strategies to mitigate potential harm.					
Vaccines	Identify mechanisms of protective immunity to HIV in newborns and infants and develop a safe and effective immunologic strategy to prevent HIV infection in this population	Evaluate genetic and antigenic variation in viruses transmitted from mothers to infants and in maternal isolates that are not transmitted; Accelerate studies of maternal-infant transmission; Develop and maintain domestic and international infrastructure necessary to enroll mothers and infants in prospective long-term followup vaccine trials; Determine the immunogenicity of various vaccines and adjuvants in newborns and infants; Determine which maternal and infant immune responses are associated with nontransmission of HIV; Identify antibody preparations for use as passive or passive/active HIV prevention; Establish criteria for advancement of candidates in Phase I, Phase II, and Phase III clinical trials; and	3,174	3,501	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Vaccines	Identify mechanisms of protective immunity to HIV in newborns and infants and develop a safe and effective immunologic strategy to prevent HIV infection in this population (continued)	Conduct Phase I, Phase II, and Phase III clinical trials of the most promising candidates that meet established criteria.					
Vaccines	Develop criteria for selection of suitable candidate vaccines, support appropriate infrastructure, and conduct Phase I and Phase II trials	Utilize vaccine selection committees to carefully evaluate promising candidates; emphasize need for thorough consideration of efficacy in animal models; Conduct Phase I and Phase II clinical trials that will determine safety and delineate comparative immunologic analysis of candidates for preventive vaccines; expand immunologic measurements to include a broad range of cell-mediated and mucosal immune responses; Conduct Phase II trials in high-risk individuals of the most promising preventive vaccine candidates or combinations that proved promising in Phase I trials conducted in low-risk individuals and that have genetic or immunologic relatedness to HIV isolates circulating in the proposed trial population; Support and maintain the AIDS Vaccine Evaluation Groups;	19,398	21,177	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Vaccines	Develop criteria for selection of suitable candidate vaccines, support appropriate infrastructure, and conduct Phase I and Phase II trials (continued)	Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with research on therapeutic AIDS vaccines, e.g., the use of candidate vaccines to ameliorate disease when administration is initiated after establishment of chronic infection; Acquire and analyze HIV isolates from recent seroconverters representative of Phase I and Phase II trial populations so that genetic and antigenic information about viruses circulating in the population can be obtained; and Conduct behavioral research pertinent to preparation for Phase III trials.					
Vaccines	Establish criteria for selection of suitable vaccine candidates and conduct Phase III clinical trials when established criteria are met	Establish criteria with concurrence of an advisory group that has the requisite scientific, public health, government, and community expertise; Conduct large-scale efficacy trials of novel preventive vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet established criteria; Evaluate HIV vaccine candidate efficacy; Evaluate multiple scientific hypotheses; and	200	229	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Vaccines	Establish criteria for selection of suitable vaccine candidates and conduct Phase III clinical trials when established criteria are met (continued)	Ensure that trials are conducted with the highest regard for social and ethical concerns of the participants.					

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

(Dollars in thousands)

Vaccines

		FY 1994 Actual	FY 1995 Appropriation	FY 1996 Pres. Bud.
Objective 1	Increase scientific knowledge about host defense mechanism and protection against HIV infection and disease.	\$43,616	\$45,735	\$47,844
Objective 2	Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models.	22,270	24,135	25,465
Objective 3	Identify appropriate domestic and international populations and develop infrastructure, including behavioral research and community education and outreach activities, that is necessary for ensuring adequate performance of Phase III efficacy clinical trials.	21,830	19,189	19,912
Objective 4	Identify mechanisms of protective immunity to HIV in newborns and infants and develop a safe and effective immunologic strategy to prevent HIV infection in this population.	3,093	3,174	3,501
Objective 5	Develop criteria for selection of suitable candidate vaccines, support appropriate infrastructure, and conduct Phase I and Phase II trials.	18,979	19,398	21,177
Objective 6	Establish criteria for selection of suitable vaccine candidates and conduct Phase III clinical trials when established criteria are met.	204	200	229
TOTAL, Vaccines		109,992	111,831	118,128

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

(Dollars in thousands)

Vaccines

		FY 1994 Estimate	FY 1995 Estimate	FY 1996 By-pass
Objective 1	Increase scientific knowledge about host defense mechanism and protection against HIV infection and disease.	\$42,960	\$44,962	\$57,506
Objective 2	Apply findings from basic, epidemiologic, and clinical research to the design and evaluation of vaccine strategies in laboratory studies and animal models.	34,214	35,329	35,473
Objective 3	Identify appropriate domestic and international populations and develop infrastructure, including behavioral research and community education and outreach activities, that is necessary for ensuring adequate performance of Phase III efficacy clinical trials.	15,333	20,392	24,361
Objective 4	Identify mechanisms of protective immunity to HIV in newborns and infants and develop a safe and effective immunologic strategy to prevent HIV infection in this population.	7,978	8,604	10,386
Objective 5	Develop criteria for selection of suitable candidate vaccines, support appropriate infrastructure, and conduct Phase I and Phase II trials.	16,419	18,480	21,424
Objective 6	Establish criteria for selection of suitable vaccine candidates and conduct Phase III clinical trials when established criteria are met.	46	50	5,621
TOTAL, Vaccines		116,950	127,817	154,771

NIH Submission - therap.

RESEARCH

Agency: National Institutes of Health

Goal: ~~Conduct and support research to~~ develop therapeutics for HIV infection and its sequelae

Objective: ^① ~~Therapeutics~~ *Identify and develop novel anti-HIV therapies.*

Action Steps: Improve screening, discovery, and preclinical development of therapeutic agents that demonstrate activity against retroviruses, fostering activity by and in collaboration with industry

Descriptions: Identify promising targets for anti-HIV therapy and extend knowledge of their mechanisms of action, develop assays for identifying drugs active against those targets, and develop new compounds active at those targets, with an emphasis placed on identifying agents active at novel targets ~~other than reverse transcriptase inhibitors;~~

Complete preclinical development, in cooperation with industry when appropriate, of promising new compounds and combinations of compounds and novel natural products, including assessment of efficacy, toxicity, teratogenicity, and fertility in animal models;

Continue and accelerate screening of large numbers of natural and synthesized compounds for anti-HIV activity in the AIDS Drug Screen, with a particular emphasis on the detection of agents ^{active against novel targets} ~~that act at unique steps of the HIV life cycle, on an understanding of the molecular basis of bioavailability and pharmacokinetics, and on ability to follow up on lead compounds for the development of analogues;~~ develop and screen combinatorial libraries; emphasize central nervous system penetration; develop formulations that would be suitable for infants and children;

Emphasize basic and applied research to advance cross-NIH development of gene therapy; support development of preclinical laboratories to advance gene therapies;

Determine the high-resolution molecular structures for several of the HIV proteins and apply these structures to the rational design of drugs as part of the targeted drug development program; determine generalizable and effective approaches for the use of macromolecular structure in designing drugs to combat HIV infection and AIDS; make resolved structures available in publicly accessible data bases;

Increase understanding of the mechanisms and limitations of drug resistance; study the effect of various agents on HIV

*Same
obj.*

replication and viral variation; evaluate early markers of resistance; evaluate the activity of anti-HIV drugs in various cell types (including macrophages) and in various stages of the cell cycle; and

Develop new compounds capable of inhibiting the sexual transmission of HIV, such as topical microbicides (which may inhibit HIV and STDs associated with enhanced HIV transmission), HIV-specific viricides, and systemic agents.

FY 95: 154,833

FY 96: 162,200

Populations Served: All populations

Constituency Involvement:

Unmet Need:

②
Objective: Therapeutics — Develop and evaluate anti-Retroviral therapies.

Action Steps: Perform clinical trials of agents active against HIV based on an understanding of pathogenesis ~~with~~ ^{emphasizing} improved design and methodologies, and integrating clinical trials with ongoing natural history studies,

Descriptions: Support and improve clinical trials of potential therapeutic agents and combinations of agents in studies to determine pharmacokinetics and bioavailability and evaluate anti-HIV combinations that are non-cross-resistant, synergistic, and toxicity-sparing and that may delay development of drug-resistant HIV strains; enhance collaboration between and within ICDS to facilitate opportunities for clinical trials;

Increase the understanding of the pathogenesis of HIV disease based on the evaluation of antiretroviral agents in clinical trials;

Implement the development and evaluation of virologic, immunologic, and clinical markers to assess drug activity and determine the prognostic value of these markers in response to therapeutic interventions;

Support research and development of clinical trials methodology and study design so that appropriate pathways are taken rapidly to evaluate the activity, clinical efficacy, and the ultimate acceptability of new agents and approaches that translate into clinical use;

Improve the utilization of GCRCs for the conduct of single and multi-institutional clinical trials;

~~Establish and expand appropriate career training programs for laboratory investigators, clinical investigators, and translational scientists.~~ [Redundant with training section]

Develop and validate quality-of-life parameters included in patient assessments of clinical trials;

Support research on the effectiveness of pharmacologic (including compliance with therapies and STD prevention) and non-pharmacologic (including psychosocial) interventions (including nutritional factors and adherence improvement);

Investigate possible interactions between therapies for HIV-related disease and other substances that HIV-infected individuals might use, such as drug abuse treatment medications, oral contraceptives or other prescription drugs, nonprescription drugs, alternative or complementary therapies, or drugs of abuse;

~~Coordinate studies to encourage co-enrollment of patients on~~

Coordinate studies to encourage co-enrollment of patients on all trials where appropriate;

~~all trials where appropriate (co-enrollment would not only allow for better utilization of limited resources but also enable assessment of concomitant medications and their interactions, improving the efficiency of the primary study);~~

known wording

Develop a coordinated plan to evaluate long-term therapeutic strategies, e.g., develop plans for long-term followup, enroll patients in sequential randomized trials once they have reached an end point in their initial trial; and

Evaluate new and existing compounds capable of inhibiting the sexual transmission of HIV, such as topical microbicides and HIV-specific viricides; nested studies to evaluate the infectivity of body fluids, such as semen and cervical secretions in trials of antiretroviral therapies.

FY 95: 145,105

FY 96: 151,627

Populations Served: All populations

Constituency Involvement:

Unmet Need:

③ Develop & evaluate immune-Restoring therapies.
Objective: Therapeutics

Action Steps: Extend our understanding of immunopathogenesis through the development and testing of strategies that enhance and/or restore the deficient immune systems of HIV-infected individuals

Descriptions: Evaluate therapeutic approaches that test specific hypotheses of HIV immunopathogenesis;

Develop and validate new methods to evaluate immune function in the context of clinical trials;

Continue and accelerate the testing of cytokines and modulators of cytokines either alone or in combination with antiretroviral agents for the purpose of reconstituting the deficient immune systems of HIV-infected individuals;

Develop and evaluate various approaches of active and passive immunotherapy for both HIV infection and its sequelae;

Develop a program of reconstituting the immune systems of HIV-infected individuals by administration of cellular elements in an autologous, syngeneic, or allogeneic fashion, including use of expanded peripheral blood T cells, bone marrow transplantation, thymic transplantation, cord blood, stem cells, and/or xenogeneic transplantation;

Develop new therapeutic strategies based on gene therapy approaches to protect or potentially reconstitute the immune system;

Use structural biologic techniques to determine the structures of various cytokines and cytokine receptors as potential targets for HIV therapies; and

Enhance collaboration among ICDs to facilitate the conduct of immune-based therapeutic trials and to enhance pathogenesis-related research in HIV-infected individuals.

FY 95: 18,619

FY 96: 19,349

Populations Served: All populations

Constituency Involvement:

Unmet Need:

④ Develop and evaluate therapies for HIV-related opportunistic infections.
Objective: Therapeutics

Action Steps: Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs and other infections modified by HIV infection, including those specific to women, children, and drug users

~~**Descriptions:** Support basic research on OIs in order to increase fundamental knowledge and to identify new therapeutic targets and strategies and understand how pathogens contribute to morbidity, such as wasting syndrome. Determine the high-resolution molecular structures for OI proteins and apply these structures to the rational design of drugs as part of the targeted drug development program and determine generalizable and effective approaches for the use of macromolecular structure in designing drugs to combat OIs associated with AIDS;~~

Support discovery and preclinical programs to develop therapies especially targeting cryptosporidia, microsporidia, JC virus, CMV, HPV, and azole-resistant fungal organisms, with emphasis on bioavailable agents with favorable pharmacokinetics. Develop *in vitro* culture systems for OIs such as *Pneumocystis carinii*;

Further conduct clinical trials for the prophylaxis and treatment of HIV-associated OIs in HIV-infected individuals, including pregnant women and children and drug users.
~~Important OIs include *Mycobacterium tuberculosis* infection (TB), *Mycobacterium avium* complex, cytomegalovirus infection, cryptosporidiosis, microsporidiosis, cryptococcal disease, azole-resistant fungal infection, toxoplasmosis, PCP, acyclovir-resistant herpes infections, progressive multifocal leukoencephalopathy (PML), bacterial infections, and other infections whose course is affected by HIV. Evaluate immune-based therapies as adjuncts for treating OIs;~~

Determine the optimal strategies and combinations of agents to prevent and treat multiple OIs (i.e., multiple opportunistic pathogen prophylaxis studies [MOPPS]), and their effects in combination with antiretroviral agents.
~~Strategies need to focus on time of initiation, compliance, pharmacologic interactions, toxicities and adverse reactions (e.g., trimethoprim-sulfamethoxazole reactions), and minimizing development of resistance; studies should include quality-of-life assessments and cost-benefit analyses;~~ out of NIH's purview.

Develop and utilize animal models for preclinical efficacy and safety testing of potential agents for OIs, including mutagenicity and teratogenicity;

Develop clinically useful assays for the rapid diagnosis,

treatment response, and sensitivity testing of OIs, especially TB, MAI, enterics, CMV, HSV, fungi, toxoplasma, and JC virus;

Support training of basic investigators, clinical investigators, and translational investigators for OI research; and

Determine the role and capability of preexisting immunity (both induced and natural) to control OI infections and the ability of HIV-infected individuals to respond to vaccination throughout the course of infection and disease.

FY 95: 107,915

FY 96: 111,887

Populations Served: All populations

Constituency Involvement:

Unmet Need:

⑤ Develop + evaluate therapies and interventions to block
Objective: Therapeutics ~ perinatal transmission.

Action Steps: Accelerate the development, evaluation, and implementation of strategies to interrupt vertical transmission of HIV from mother to child

Descriptions: Support the rapid translation of basic research observations to strategies for the interruption of vertical transmission; apply the results of clinical trials to the investigation of pathogenesis and to clinical practice;

Develop strategies and agents to interrupt the vertical transmission of HIV from pregnant women to their offspring, ~~including antiviral agents, anti-HIV immunoglobulin, and monoclonal antibodies, HIV vaccines, adjuvants, virucides, and other intrapartum interventions,~~ explore the potential of combined strategies; evaluate the safety, toxicity, pharmacokinetics, and antiretroviral activity of anti-HIV agents in pregnant women and newborns;

Expand the obstetrical and pediatric infrastructure for the conduct of perinatal trials through collaborative efforts, both national and international;

Support the long-term followup of all women and children who participate in perinatal trials to evaluate potential distant effects of antiretroviral agents and/or biologicals;

Investigate the role of the placenta in transmission of anti-HIV drugs from mother to fetus;

Develop and improve sensitive and specific diagnostic parameters that are cost-effective to permit early differentiation of HIV-infection status in children born to HIV-infected mothers;

Assess the potential efficacy and feasibility of obstetric interventions to prevent vertical transmissions, such as cesarean deliveries and other aspects of intrapartum care;

Evaluate the risk of vertical transmission of drug-resistant virus; and

Evaluate factors that contribute to or protect against vertical transmission; develop effective strategies that could more easily be afforded globally to help reduce vertical transmission and perhaps decrease transmission via breast milk.

FY 95: 5,690

FY 96: 6,138

Populations Served: All populations

Constituency Involvement:

Unmet Need:

⑥ Develop and evaluate therapies for HIV-related malignancies.
Objective: Therapeutics

Action Steps: Target the discovery, development, and clinical evaluation of improved therapeutic strategies for the treatment and prevention of HIV-associated malignancies based on an understanding of pathogenesis

Descriptions: ~~Support basic research on HIV-associated malignancies to increase fundamental knowledge of the etiology, pathogenesis, and biology of these neoplasms; develop preclinical models for testing potential therapeutic strategies;~~

Identify novel mechanisms and targets (e.g., cytokines, angiogenesis, viral or hormonal cofactors) for treatment and prevention of HIV-associated tumors, including Kaposi's sarcoma, non-Hodgkin's lymphoma, HPV-associated malignancies, and others, and develop new therapeutic strategies on the basis of these findings;

Use structural biologic and biochemical information to rationally design drugs to inhibit specific pathogenic factors of HIV-associated malignancies (e.g., oncoprotein of HPV);

Encourage the development and coordinate the conduct of clinical trials that concurrently evaluate therapeutic strategies directed against the malignancy with anti-retroviral and anti-OI strategies in order to assess the effects of such treatment on the malignancy as well as on the underlying HIV infection, immune function, and clinical course;

Continue and expand screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies ~~(e.g., agents with better CNS penetration, agents with better safety profiles);~~

Develop trials to optimize existing therapies for malignancies in HIV-infected patients, ~~including therapeutic adjuncts such as hematopoietic colony-stimulating factors and supportive care; develop and validate quality of life assessments;~~

Encourage collaborative studies to develop mechanisms for early identification of patients at high risk for malignancy and to develop and assess interventional strategies to reduce or prevent the development of malignancies;

Support training of basic investigators, clinical investigators, and translational scientists for research of malignancies in HIV-infected patients;

Improve diagnostic methods for early diagnosis of

malignancies and for early detection of recurrent cancer;

Coordinate referral of patients with malignancy end points on other studies to malignancy trials; and

Improve collaboration between various adult and pediatric cooperative groups conducting clinical trials of HIV-associated malignancies and ICDs and industry to accelerate trials completion and approval of active agents.

FY 95: 16,642

FY 96: 16,939

Populations Served: All populations

Constituent Involvement:

Unmet Need:

Objective: ^{(7) Develop + evaluate therapies for HIV-related neurologic disease.} ~~Therapeutics~~

Action Steps: Develop an understanding of the neuropathogenesis of HIV infection and strategies for assessing, preventing, and treating neurologic disease in the course HIV infection

~~**Descriptions:** Develop an improved understanding of the biology and epidemiology of neurologic disease in HIV-infected individuals,~~

Develop novel strategies and agents that are active against putative pathways of HIV-induced CNS dysfunction, ~~e.g., inhibitors of quinolinic acid, excitatory neurotransmitters, gp160/120, and other potential neurotoxins,~~

Implement studies related to the delineation of mechanisms responsible for impaired neurocognitive development in children born to HIV-infected mothers, and develop strategies directed at the prevention and treatment of this complication of HIV infection;

Implement clinical trials addressing nervous system complications of HIV infection and incorporate neurologic assessments into other HIV-related clinical trials;

Develop therapeutic agents that are capable of crossing the blood-brain barrier and are active against HIV infection in relevant cells in the CNS; develop an understanding of mechanisms involved in penetration of the blood-brain barrier;

Better delineate etiologies of peripheral neuropathy in HIV infection, and develop strategies to prevent and treat this complication;

Develop and utilize *in vitro* and animal models of CNS impairment and ADC to further identify agents that can reverse HIV neuropathogenesis; and

Implement assessments and approaches for the diagnosis of HIV-related dementia in clinical studies; ~~implement standardized adult and pediatric neuropsychologic and neurologic assessment batteries in clinical studies and evaluate treatment-induced changes in neurocognitive impairment in a linguistically and culturally sensitive context.~~

FY 95: 11,614

FY 96: 12,268

Populations Served: All populations

Constituency Involvement:

Unmet Need:

⑧ Develop + evaluate therapies for HIV-related complications.
Objective: Therapeutics

Action Steps: Develop therapies for the treatment and prevention of serious HIV-associated complications, including wasting syndrome, growth failure, metabolic disorders, dermatologic disorders, ITP, nephropathy, oral diseases, and other symptoms and serious complications

Descriptions: ~~Support research into the biology of the various clinical sequelae of HIV infection (above);~~

Develop and evaluate therapeutic strategies to ameliorate the various sequelae of HIV infection (above) based on an increased understanding of pathogenesis;

Develop and evaluate therapeutic strategies for alleviating the various symptoms of unclear etiology in HIV-infected persons (above) and improving the quality of life; and

Develop and validate quality-of-life parameters for the various sequelae of HIV infection (above).

FY 95: 12,844

FY 96: 15,431

Populations Served: All populations

Constituent Involvement:

Unmet Need:

	95	96	Bypass
1	154,833	162,200	134,980
2	145,105	151,627	216,181
3	18,619	19,349	21,779 *
4	107,915	111,887	97,787
5	5,690	6,138	29,474
6	16,642	16,939	17,430
7	11,614	12,268	11,658 *
8	12,844	15,431	16,116
		495,839	545,405
			△ 49,566

Strategy Therap.

RESEARCH

Agency: National Institutes of Health

Goal: Develop and evaluate therapies for HIV infection and its sequelae.

Objective 1: Identify and develop novel anti-HIV therapies.

Action Steps: Improve screening, discovery, and preclinical development of therapeutic agents that demonstrate activity against retroviruses, fostering activity by and in collaboration with industry.

Descriptions: Identify promising targets for anti-HIV therapy and extend knowledge of their mechanisms of action, develop assays for identifying drugs active against those targets, and develop new compounds active at those targets, with an emphasis placed on identifying agents active at novel targets;

Complete preclinical development, in cooperation with industry when appropriate, of promising new compounds and combinations of compounds and novel natural products, including assessment of efficacy, toxicity, teratogenicity, and fertility in animal models;

Continue and accelerate screening of large numbers of natural and synthesized compounds for anti-HIV activity in the AIDS Drug Screen, with a particular emphasis on the detection of agents active against novel targets; develop and screen combinatorial libraries; emphasize central nervous system penetration; develop formulations that would be suitable for infants and children;

Emphasize basic and applied research to advance cross-NIH development of gene therapy; support development of preclinical laboratories to advance gene therapies;

Determine the high-resolution molecular structures for several of the HIV proteins and apply these structures to the rational design of drugs as part of the targeted drug development program; determine generalizable and effective approaches for the use of macromolecular structure in designing drugs to combat HIV infection and AIDS; make resolved structures available in publicly accessible data bases;

Increase understanding of the mechanisms and limitations of drug resistance; study the effect of various agents on HIV replication and viral variation; evaluate early markers of resistance; evaluate the activity of anti-HIV drugs in various cell types (including macrophages) and in various stages of the cell cycle; and

Develop new compounds capable of inhibiting the sexual transmission of HIV, such as topical microbicides (which may inhibit HIV and STDs associated with enhanced HIV transmission), HIV-specific viricides, and systemic agents.

Objective 2: Develop and evaluate anti-retroviral therapies.

Action Steps: Perform clinical trials of agents active against HIV based on an understanding of pathogenesis, emphasizing emphasis on improved design and methodologies, and integrating clinical trials with ongoing natural history studies.

Descriptions: Support and improve clinical trials of potential therapeutic agents and combinations of agents in studies to determine pharmacokinetics and bioavailability and evaluate anti-HIV combinations that are non-cross-resistant, synergistic, and toxicity-sparing and that may delay development of drug-resistant HIV strains; enhance collaboration between and within ICDCs to facilitate opportunities for clinical trials;

Increase the understanding of the pathogenesis of HIV disease based on the evaluation of antiretroviral agents in clinical trials;

Implement the development and evaluation of virologic, immunologic, and clinical markers to assess drug activity and determine the prognostic value of these markers in response to therapeutic interventions;

Support research and development of clinical trials methodology and study design so that appropriate pathways are taken rapidly to evaluate the activity, clinical efficacy, and the ultimate acceptability of new agents and approaches that translate into clinical use;

Improve the utilization of GCRCs for the conduct of single and multi-institutional clinical trials;

Develop and validate quality-of-life parameters included in patient assessments of clinical trials;

Support research on the effectiveness of pharmacologic (including compliance with therapies and STD prevention) and non-pharmacologic (including psychosocial) interventions (including nutritional factors and adherence improvement);

Investigate possible interactions between therapies for HIV-related disease and other substances that HIV-infected individuals might use, such as drug abuse treatment medications, oral contraceptives or other prescription drugs, nonprescription drugs, alternative or complementary

therapies, or drugs of abuse;

Coordinate studies to encourage co-enrollment of patients on all trials where appropriate;

Develop a coordinated plan to evaluate long-term therapeutic strategies, e.g., develop plans for long-term followup, enroll patients in sequential randomized trials once they have reached an end point in their initial trial; and

Evaluate new and existing compounds capable of inhibiting the sexual transmission of HIV, such as topical microbicides and HIV-specific viricides; nested studies to evaluate the infectivity of body fluids, such as semen and cervical secretions in trials of antiretroviral therapies.

Objective 3: Develop and evaluate immune-restoring therapies.

Action Steps: Extend our understanding of immunopathogenesis through the development and testing of strategies that enhance and/or restore the deficient immune systems of HIV-infected individuals.

Descriptions: Evaluate therapeutic approaches that test specific hypotheses of HIV immunopathogenesis;

Develop and validate new methods to evaluate immune function in the context of clinical trials;

Continue and accelerate the testing of cytokines and modulators of cytokines either alone or in combination with antiretroviral agents for the purpose of reconstituting the deficient immune systems of HIV-infected individuals;

Develop and evaluate various approaches of active and passive immunotherapy for both HIV infection and its sequelae;

Develop a program of reconstituting the immune systems of HIV-infected individuals by administration of cellular elements in an autologous, syngeneic, or allogeneic fashion, including use of expanded peripheral blood T cells, bone marrow transplantation, thymic transplantation, cord blood, stem cells, and/or xenogeneic transplantation;

Develop new therapeutic strategies based on gene therapy approaches to protect or potentially reconstitute the immune system;

Use structural biologic techniques to determine the structures of various cytokines and cytokine receptors as potential targets for HIV therapies; and

Enhance collaboration among ICDs to facilitate the conduct

of immune-based therapeutic trials and to enhance pathogenesis-related research in HIV-infected individuals.

Objective 4: Develop and evaluate therapies for HIV-related opportunistic infections.

Action Steps: Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs and other infections modified by HIV infection, including those specific to women, children, and drug users.

Descriptions: Support discovery and preclinical programs to develop therapies especially targeting cryptosporidia, microsporidia, JC virus, CMV, HPV, and azole-resistant fungal organisms, with emphasis on bioavailable agents with favorable pharmacokinetics. Develop *in vitro* culture systems for OIs;

Further conduct clinical trials for the prophylaxis and treatment of HIV-associated OIs in HIV-infected individuals, including pregnant women and children and drug users. Evaluate immune-based therapies as adjuncts for treating OIs;

Determine the optimal strategies and combinations of agents to prevent and treat multiple OIs (i.e., multiple opportunistic pathogen prophylaxis studies [MOPPS]), and their effects in combination with antiretroviral agents.

Develop and utilize animal models for preclinical efficacy and safety testing of potential agents for OIs, including mutagenicity and teratogenicity;

Develop clinically useful assays for the rapid diagnosis, treatment response, and sensitivity testing of OIs;

Support training of basic investigators, clinical investigators, and translational investigators for OI research; and

Determine the role and capability of preexisting immunity (both induced and natural) to control OI infections and the ability of HIV-infected individuals to respond to vaccination throughout the course of infection and disease.

Objective 5: Develop and evaluate therapies^{and} interventions to block perinatal transmission.

Action Steps: Accelerate the development, evaluation, and implementation of strategies to interrupt vertical transmission of HIV from mother to child.

Descriptions: Support the rapid translation of basic

research observations to strategies for the interruption of vertical transmission; apply the results of clinical trials to the investigation of pathogenesis and to clinical practice;

Develop strategies and agents to interrupt the vertical transmission of HIV from pregnant women to their offspring; explore the potential of combined strategies; evaluate the safety, toxicity, pharmacokinetics, and antiretroviral activity of anti-HIV agents in pregnant women and newborns;

Expand the obstetrical and pediatric infrastructure for the conduct of perinatal trials through collaborative efforts, both national and international;

Support the long-term followup of all women and children who participate in perinatal trials to evaluate potential distant effects of antiretroviral agents and/or biologicals;

Investigate the role of the placenta in transmission of anti-HIV drugs from mother to fetus;

Develop and improve sensitive and specific diagnostic parameters that are cost-effective to permit early differentiation of HIV-infection status in children born to HIV-infected mothers;

Assess the potential efficacy and feasibility of obstetric interventions to prevent vertical transmissions, such as cesarean deliveries and other aspects of intrapartum care;

Evaluate the risk of vertical transmission of drug-resistant virus; and

Evaluate factors that contribute to or protect against vertical transmission; develop effective strategies that could more easily be afforded globally to help reduce vertical transmission and perhaps decrease transmission via breast milk.

Objective 6: Develop and evaluate therapies for HIV-related malignancies.

Action Steps: Target the discovery, development, and clinical evaluation of improved therapeutic strategies for the treatment and prevention of HIV-associated malignancies based on an understanding of pathogenesis.

Descriptions: Identify novel mechanisms and targets (e.g., cytokines, angiogenesis, viral or hormonal cofactors) for treatment and prevention of HIV-associated tumors, including Kaposi's sarcoma, non-Hodgkin's lymphoma, HPV-associated malignancies, and others, and develop new therapeutic strategies on the basis of these findings;

Use structural biologic and biochemical information to rationally design drugs to inhibit specific pathogenic factors of HIV-associated malignancies;

Encourage the development and coordinate the conduct of clinical trials that concurrently evaluate therapeutic strategies directed against the malignancy with anti-retroviral and anti-OI strategies in order to assess the effects of such treatment on the malignancy as well as on the underlying HIV infection, immune function, and clinical course;

Continue and expand screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies;

Develop trials to optimize existing therapies for malignancies in HIV-infected patients;

Encourage collaborative studies to develop mechanisms for early identification of patients at high risk for malignancy and to develop and assess interventional strategies to reduce or prevent the development of malignancies;

Support training of basic investigators, clinical investigators, and translational scientists for research of malignancies in HIV-infected patients;

Improve diagnostic methods for early diagnosis of malignancies and for early detection of recurrent cancer;

Coordinate referral of patients with malignancy end points on other studies to malignancy trials; and

Improve collaboration between various adult and pediatric cooperative groups conducting clinical trials of HIV-associated malignancies and ICDs and industry to accelerate trials completion and approval of active agents.

Objective 7: Develop and evaluate therapies for HIV-related neurologic disease.

Action Steps: Develop an understanding of the neuropathogenesis of HIV infection and strategies for assessing, preventing, and treating neurologic disease in the course of HIV infection.

Descriptions: Develop novel strategies and agents that are active against putative pathways of HIV-induced CNS dysfunction;

Implement studies related to the delineation of mechanisms responsible for impaired neurocognitive development in children born to HIV-infected mothers, and develop

strategies directed at the prevention and treatment of this complication of HIV infection;

Implement clinical trials addressing nervous system complications of HIV infection and incorporate neurologic assessments into other HIV-related clinical trials;

Develop therapeutic agents that are capable of crossing the blood-brain barrier and are active against HIV infection in relevant cells in the CNS; develop an understanding of mechanisms involved in penetration of the blood-brain barrier;

Better delineate etiologies of peripheral neuropathy in HIV infection, and develop strategies to prevent and treat this complication;

Develop and utilize *in vitro* and animal models of CNS impairment and ADC to further identify agents that can reverse HIV neuropathogenesis; and

Implement assessments and approaches for the diagnosis of HIV-related dementia in clinical studies.

Objective 8: Develop and evaluate therapies for HIV-related complications.

Action Steps: Develop an understanding of HIV-associated complications, including wasting syndrome, growth failure, metabolic disorders, dermatologic disorders, ITP, nephropathy, oral diseases, and other symptoms and serious complications.

Descriptions: Develop and evaluate therapeutic strategies to ameliorate the various sequelae of HIV infection based on an increased understanding of pathogenesis;

Develop and evaluate therapeutic strategies for alleviating the various symptoms of unclear etiology in HIV-infected persons and improving the quality of life; and

Develop and validate quality-of-life parameters for the various sequelae of HIV infection.

FY 95: 473,262

FY 96: 495,839

Populations Served: All populations

Constituency Involvement: Researchers, clinicians, community and patient representatives, NIAID Advisory Council, ARAC, and OAR Advisory Committees. Others?

Unmet Needs: The NIH FY 1996 Plan and Budget Estimate for

Scientific Opportunities in HIV-Related Research identified areas for further productive research in this area in the amount of \$49,566 over the FY 96 figure.

A v. B.

CWC.

RESEARCH

Agency: National Institutes of Health

Goal: Develop and evaluate therapies for HIV infection and its sequelae.

Objective 1: Identify and develop novel anti-HIV therapies.
~~Conduct and support research to develop therapeutics for HIV infection and its sequelae~~

Objective: ~~Therapeutics~~

Action Steps: Improve screening, discovery, and preclinical development of therapeutic agents that demonstrate activity against retroviruses, fostering activity by and in collaboration with industry.

Descriptions: Identify promising targets for anti-HIV therapy and extend knowledge of their mechanisms of action, fostering activity by and in collaboration with industry

Descriptions: ~~Identify promising targets for anti HIV therapy and extend knowledge of their mechanisms of action, develop assays for identifying drugs active against those targets, and develop new compounds active at those targets, with an emphasis placed on identifying agents active at novel targets; with an emphasis placed on identifying agents active at novel targets other than reverse transcriptase inhibitors;~~

Complete preclinical development, in cooperation with industry when appropriate, of promising new compounds and combinations of compounds and novel natural products, including assessment of efficacy, toxicity, teratogenicity, and fertility in animal models;

Continue and accelerate screening of large numbers of natural and synthesized compounds for anti-HIV activity in the AIDS Drug Screen, with a particular emphasis on the detection of agents active against novel targets; ~~with a particular emphasis on the detection of agents that act at unique steps of the HIV life cycle, on an understanding of the molecular basis of bioavailability and pharmacokinetics, and on ability to follow up on lead compounds for the development of analogues;~~ develop and screen combinatorial libraries; emphasize central nervous system penetration; develop formulations that would be suitable for infants and children;

Emphasize basic and applied research to advance cross-NIH development of gene therapy; support development of preclinical laboratories to advance gene therapies;

Determine the high-resolution molecular structures for several of the HIV proteins and apply these structures to the rational design of drugs as part of the targeted drug development program; determine generalizable and effective approaches for the use of macromolecular structure in designing drugs to combat HIV infection and AIDS; make resolved structures available in publicly accessible data bases;

Increase understanding of the mechanisms and limitations of drug resistance; study the effect of various agents on HIV replication and viral variation; evaluate early markers of resistance; evaluate the activity of anti-HIV drugs in various cell types (including macrophages) and in various stages of the cell cycle; and

Develop new compounds capable of inhibiting the sexual transmission of HIV, such as topical microbicides (which may inhibit HIV and STDs associated with enhanced HIV transmission), HIV-specific viricides, and systemic agents.

Objective 2: Develop and evaluate anti-retroviral therapies.

Action Steps: Perform clinical trials of agents active against HIV based on an understanding of pathogenesis, emphasizing emphasis on improved design and methodologies, and integrating clinical trials with ongoing natural history studies.

FY 95: 154,833

FY 96: 162,200

Populations Served: All populations

Constituency Involvement:—

Unmet Need:—

Objective: Therapeutics

~~**Action Steps:** Perform clinical trials of agents active against HIV based on an understanding of pathogenesis with emphasis on improved design and methodologies, and integrate clinical trials with ongoing natural history studies~~

Descriptions: Support and improve clinical trials of potential therapeutic agents and combinations of agents in studies to determine pharmacokinetics and bioavailability and evaluate anti-HIV combinations that are non-cross-resistant, synergistic, and toxicity-sparing and that may delay development of drug-resistant HIV strains; enhance collaboration between and within ICDS to facilitate opportunities for clinical trials;

Increase the understanding of the pathogenesis of HIV disease based on the evaluation of antiretroviral agents in clinical trials;

Implement the development and evaluation of virologic, immunologic, and clinical markers to assess drug activity and determine the prognostic value of these markers in response to therapeutic interventions;

Support research and development of clinical trials methodology and study design so that appropriate pathways are taken rapidly to evaluate the activity, clinical efficacy, and the ultimate acceptability of new agents and approaches that translate into clinical use;

Improve the utilization of GCRCs for the conduct of single and multi-institutional clinical trials;

~~Establish and expand appropriate career training programs for laboratory investigators, clinical investigators, and translational scientists;~~

Develop and validate quality-of-life parameters included in patient assessments of clinical trials;

Support research on the effectiveness of pharmacologic (including compliance with therapies and STD prevention) and non-pharmacologic (including psychosocial) interventions (including nutritional factors and adherence improvement);

Investigate possible interactions between therapies for HIV-related disease and other substances that HIV-infected individuals might use, such as drug abuse treatment medications, oral contraceptives or other prescription drugs, nonprescription drugs, alternative or complementary therapies, or drugs of abuse;

Coordinate studies to encourage co-enrollment of patients on

~~all trials where appropriate; Coordinate studies to encourage co-enrollment of patients on all trials where appropriate (co-enrollment would not only allow for better utilization of limited resources but also enable assessment of concomitant medications and their interactions, improving the efficiency of the primary study);~~

Develop a coordinated plan to evaluate long-term therapeutic strategies, e.g., develop plans for long-term followup, enroll patients in sequential randomized trials once they have reached an end point in their initial trial; and

Evaluate new and existing compounds capable of inhibiting the sexual transmission of HIV, such as topical microbicides and HIV-specific viricides; nested studies to evaluate the infectivity of body fluids, such as semen and cervical secretions in trials of antiretroviral therapies.

Objective 3: Develop and evaluate immune-restoring therapies.

Action Steps: Extend our understanding of immunopathogenesis through the development and testing of strategies that enhance and/or restore the deficient immune systems of HIV-infected individuals.

~~FY 95: 145,105~~

~~FY 96: 151,627~~

~~Populations Served: All populations~~

~~Constituency Involvement:~~

~~Unmet Need:~~

~~Objective: Therapeutics~~

~~Action Steps:~~ ~~Extend our understanding of immunopathogenesis through the development and testing of strategies that enhance and/or restore the deficient immune systems of HIV-infected individuals~~

Descriptions: Evaluate therapeutic approaches that test specific hypotheses of HIV immunopathogenesis;

Develop and validate new methods to evaluate immune function in the context of clinical trials;

Continue and accelerate the testing of cytokines and modulators of cytokines either alone or in combination with antiretroviral agents for the purpose of reconstituting the deficient immune systems of HIV-infected individuals;

Develop and evaluate various approaches of active and passive immunotherapy for both HIV infection and its sequelae;

Develop a program of reconstituting the immune systems of HIV-infected individuals by administration of cellular elements in an autologous, syngeneic, or allogeneic fashion, including use of expanded peripheral blood T cells, bone marrow transplantation, thymic transplantation, cord blood, stem cells, and/or xenogeneic transplantation;

Develop new therapeutic strategies based on gene therapy approaches to protect or potentially reconstitute the immune system;

Use structural biologic techniques to determine the structures of various cytokines and cytokine receptors as potential targets for HIV therapies; and

Enhance collaboration among ICDs to facilitate the conduct of immune-based therapeutic trials and to enhance pathogenesis-related research in HIV-infected individuals.

Objective 4: Develop and evaluate therapies for HIV-related opportunistic infections.

~~FY 95: 18,619~~

~~FY 96: 19,349~~

~~Populations Served: All populations~~

~~Constituency Involvement:~~

~~Unmet Need:~~

Objective: Therapeutics

Action Steps: Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs and other infections modified by HIV infection, including those specific to women, children, and drug users.

Descriptions: Support discovery and preclinical programs to develop therapies especially targeting cryptosporidia, and drug users

Descriptions: Support basic research on OIs in order to increase fundamental knowledge and to identify new therapeutic targets and strategies and understand how pathogens contribute to morbidity, such as wasting syndrome. Determine the high resolution molecular structures for OI proteins and apply these structures to the rational design of drugs as part of the targeted drug development program and determine generalizable and effective approaches for the use of macromolecular structure in designing drugs to combat OIs associated with AIDS;

Support discovery and preclinical programs to develop therapies especially targeting cryptosporidia, microsporidia, JC virus, CMV, HPV, and azole-resistant fungal organisms, with emphasis on bioavailable agents with favorable pharmacokinetics. Develop in vitro culture systems for OIs; Develop in vitro culture systems for OIs such as *Pneumocystis carinii*;

Further conduct clinical trials for the prophylaxis and treatment of HIV-associated OIs in HIV-infected individuals, including pregnant women and children and drug users.— Important OIs include *Mycobacterium tuberculosis* infection (TB), *Mycobacterium avium* complex, cytomegalovirus infection, cryptosporidiosis, microsporidiosis, cryptococcal disease, azole resistant fungal infection, toxoplasmosis, PCP, acyclovir resistant herpes infections, progressive multifocal leukoencephalopathy (PML), bacterial infections, and other infections whose course is affected by HIV. Evaluate immune-based therapies as adjuncts for treating OIs;

Determine the optimal strategies and combinations of agents to prevent and treat multiple OIs (i.e., multiple opportunistic pathogen prophylaxis studies [MOPPS]), and their effects in combination with antiretroviral agents.— Strategies need to focus on time of initiation, compliance, pharmacologic interactions, toxicities and adverse reactions (e.g., trimethoprim sulfamethoxazole reactions), and minimizing development of resistance; studies should include quality of life assessments and cost benefit analyses;

Develop and utilize animal models for preclinical efficacy and safety testing of potential agents for OIs, including mutagenicity and teratogenicity;

Develop clinically useful assays for the rapid diagnosis, treatment response, and sensitivity testing of OIs, and sensitivity testing of OIs, especially TB, MAI, enterics, CMV, HSV, fungi, toxoplasma, and JC virus;

Support training of basic investigators, clinical investigators, and translational investigators for OI research; and

Determine the role and capability of preexisting immunity (both induced and natural) to control OI infections and the ability of HIV-infected individuals to respond to vaccination throughout the course of infection and disease.

Objective 5: Develop and evaluate therapies interventions to block perinatal transmission.

~~FY 95: 107,915~~

~~FY 96: 111,887~~

~~Populations Served: All populations~~

~~Constituency Involvement:~~

~~Unmet Need:~~

Objective: Therapeutics

Action Steps: Accelerate the development, evaluation, and implementation of strategies to interrupt vertical transmission of HIV from mother to child;
~~and implementation of strategies to interrupt vertical transmission of HIV from mother to child~~

Descriptions: Support the rapid translation of basic research observations to strategies for the interruption of vertical transmission; apply the results of clinical trials to the investigation of pathogenesis and to clinical practice;

~~Develop strategies and agents to interrupt the vertical transmission of HIV from pregnant women to their offspring;~~
~~Develop strategies and agents to interrupt the vertical transmission of HIV from pregnant women to their offspring, including antiviral agents, anti HIV immunoglobulin, and monoclonal antibodies, HIV vaccines, adjuvants, virucides, and other intrapartum interventions; explore the potential of combined strategies; evaluate the safety, toxicity, pharmacokinetics, and antiretroviral activity of anti-HIV agents in pregnant women and newborns;~~

Expand the obstetrical and pediatric infrastructure for the conduct of perinatal trials through collaborative efforts, both national and international;

Support the long-term followup of all women and children who participate in perinatal trials to evaluate potential distant effects of antiretroviral agents and/or biologicals;

Investigate the role of the placenta in transmission of anti-HIV drugs from mother to fetus;

Develop and improve sensitive and specific diagnostic parameters that are cost-effective to permit early differentiation of HIV-infection status in children born to HIV-infected mothers;

Assess the potential efficacy and feasibility of obstetric interventions to prevent vertical transmissions, such as cesarean deliveries and other aspects of intrapartum care;

Evaluate the risk of vertical transmission of drug-resistant virus; and

Evaluate factors that contribute to or protect against vertical transmission; develop effective strategies that could more easily be afforded globally to help reduce vertical transmission and perhaps decrease transmission via

breast milk.

Objective 6: Develop and evaluate therapies for HIV-related malignancies.

Action Steps: Target the discovery, development, and clinical evaluation of improved therapeutic strategies for the treatment and prevention of HIV-associated malignancies based on an understanding of pathogenesis.

Descriptions: Identify novel mechanisms and targets (e. ~~FY~~
~~95: 5,690~~
~~FY 96: 6,138~~

~~Populations Served:~~ All populations

~~Constituency Involvement:~~

~~Constituency Involvement: Constituency Involvement:—~~

~~Unmet Need:—~~

Objective: Therapeutics

Action Steps: Target the discovery, development, and clinical evaluation of improved therapeutic strategies for the treatment and prevention of HIV-associated malignancies based on an understanding of pathogenesis

Descriptions: Support basic research on HIV-associated malignancies to increase fundamental knowledge of the etiology, pathogenesis, and biology of these neoplasms; develop preclinical models for testing potential therapeutic strategies;

Identify novel mechanisms and targets (e.g., cytokines, angiogenesis, viral or hormonal cofactors) for treatment and prevention of HIV-associated tumors, including Kaposi's sarcoma, non-Hodgkin's lymphoma, HPV-associated malignancies, and others, and develop new therapeutic strategies on the basis of these findings;

Use structural biologic and biochemical information to rationally design drugs to inhibit specific pathogenic factors of HIV-associated malignancies; Use structural biologic and biochemical information to rationally design drugs to inhibit specific pathogenic factors of HIV-associated malignancies (e.g., oncoprotein of HPV);

Encourage the development and coordinate the conduct of clinical trials that concurrently evaluate therapeutic strategies directed against the malignancy with anti-retroviral and anti-OI strategies in order to assess the effects of such treatment on the malignancy as well as on the underlying HIV infection, immune function, and clinical course;

Continue and expand screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies;

Develop trials to optimize existing therapies for malignancies in HIV-infected patients; and development of novel therapeutic agents with activity against HIV-associated malignancies (e.g., agents with better CNS penetration, agents with better safety profiles);

Develop trials to optimize existing therapies for malignancies in HIV-infected patients, including therapeutic

~~adjuncts such as hematopoietic colony stimulating factors and supportive care; develop and validate quality of life assessments;~~

Encourage collaborative studies to develop mechanisms for early identification of patients at high risk for malignancy and to develop and assess interventional strategies to reduce or prevent the development of malignancies;

Support training of basic investigators, clinical investigators, and translational scientists for research of malignancies in HIV-infected patients;

Improve diagnostic methods for early diagnosis of malignancies and for early detection of recurrent cancer;

Coordinate referral of patients with malignancy end points on other studies to malignancy trials; and

Improve collaboration between various adult and pediatric cooperative groups conducting clinical trials of HIV-associated malignancies and ICDs and industry to accelerate trials completion and approval of active agents.

Objective 7: Develop and evaluate therapies for HIV-related neurologic disease.

~~FY 95: 16,642~~

~~FY 96: 16,939~~

~~**Populations Served:** All populations~~

~~**Constituent Involvement:**~~

~~**Unmet Need:**~~

Objective: Therapeutics

Action Steps: Develop an understanding of the neuropathogenesis of HIV infection and strategies for assessing, preventing, and treating neurologic disease in the course of HIV infection.

Descriptions: Develop novel strategies and agents that are active against putative pathways of HIV-induced CNS dysfunction; and treating neurologic disease in the course HIV infection

Descriptions: Develop an improved understanding of the biology and epidemiology of neurologic disease in HIV-infected individuals;

Develop novel strategies and agents that are active against putative pathways of HIV induced CNS dysfunction, e.g., inhibitors of quinolinic acid, excitatory neurotransmitters, gp160/120, and other potential neurotoxins;

Implement studies related to the delineation of mechanisms responsible for impaired neurocognitive development in children born to HIV-infected mothers, and develop strategies directed at the prevention and treatment of this complication of HIV infection;

Implement clinical trials addressing nervous system complications of HIV infection and incorporate neurologic assessments into other HIV-related clinical trials;

Develop therapeutic agents that are capable of crossing the blood-brain barrier and are active against HIV infection in relevant cells in the CNS; develop an understanding of mechanisms involved in penetration of the blood-brain barrier;

Better delineate etiologies of peripheral neuropathy in HIV infection, and develop strategies to prevent and treat this complication;

Develop and utilize *in vitro* and animal models of CNS impairment and ADC to further identify agents that can reverse HIV neuropathogenesis; and

Implement assessments and approaches for the diagnosis of HIV-related dementia in clinical studies.

Objective 8: Develop and evaluate therapies for HIV-related complications.

Action Steps: Develop an understanding of HIV-associated complications, Implement assessments and approaches for the diagnosis of HIV related dementia in clinical

~~studies; implement standardized adult and
pediatric neuropsychologic and neurologic
assessment batteries in clinical studies and
evaluate treatment induced changes in
neurocognitive impairment in a linguistically
and culturally sensitive context.~~

~~FY 95: 11,614~~

~~FY 96: 12,268~~

~~Populations Served: All populations~~

~~Constituency Involvement:~~

~~Unmet Need:~~

~~Unmet Need:Unmet Need:~~

Objective: Therapeutics

Action Steps: Develop therapies for the treatment and prevention of serious HIV-associated complications, including wasting syndrome, growth failure, metabolic disorders, dermatologic disorders, ITP, nephropathy, oral diseases, and other symptoms and serious complications.

Descriptions: Develop and evaluate therapeutic strategies to ameliorate the various sequelae of HIV infection based on an increased understanding of pathogenesis;

Develop and evaluate therapeutic strategies for alleviating the various symptoms of unclear etiology in HIV-infected persons and improving the quality of life; and

Develop and validate quality-of-life parameters for the various sequelae of HIV infection.

FY 95: 473,262

FY 96: 495,839

Populations Served: All populations

Constituency Involvement: Researchers, clinicians, community and patient representatives, NIAID Advisory Council, ARAC, and OAR Advisory Committees. Others?

Unmet Needs: The NIH FY 1996 Plan and Budget Estimate for Scientific Opportunities in HIV-Related Research identified areas for further productive research in this area in the amount of \$49,566 over the FY 96 figure.

~~and other symptoms and serious complications~~

Descriptions: Support research into the biology of the various clinical sequelae of HIV infection (above);

Develop and evaluate therapeutic strategies to ameliorate the various sequelae of HIV infection (above) based on an increased understanding of pathogenesis;

Develop and evaluate therapeutic strategies for alleviating the various symptoms of unclear etiology in HIV-infected persons (above) and improving the quality of life; and

Develop and validate quality of life parameters for the various sequelae of HIV infection (above).

FY 95: 12,844

FY 96: 15,431

Populations Served: All populations

Constituent Involvement:

~~Unmet Need:~~

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Area Research

Goal 3 Conduct and support research to develop therapeutics for HIV infection and its sequelae

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics	Improve screening, discovery, and preclinical development of therapeutic agents that demonstrate activity against retroviruses, fostering activity by and in collaboration with industry	Identify promising targets for anti-HIV therapy and extend knowledge of their mechanisms of action, develop assays for identifying drugs active against those targets, and develop new compounds active at those targets, with an emphasis placed on identifying agents active at novel targets other than reverse transcriptase inhibitors; Complete preclinical development, in cooperation with industry when appropriate, of promising new compounds and combinations of compounds and novel natural products, including assessment of efficacy, toxicity, teratogenicity, and fertility in animal models;	154,833	162,200	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics	Improve screening, discovery, and preclinical development of therapeutic agents that demonstrate activity against retroviruses, fostering activity by and in collaboration with industry (continued)	Continue and accelerate screening of large numbers of natural and synthesized compounds for anti-HIV activity in the AIDS Drug Screen, with a particular emphasis on the detection of agents that act at unique steps of the HIV life cycle, on an understanding of the molecular basis of bioavailability and pharmacokinetics, and on ability to follow up on lead compounds for the development of analogues; develop and screen combinatorial libraries; emphasize central nervous system penetration; develop formulations that would be suitable for infants and children; Emphasize basic and applied research to advance cross-NIH development of gene therapy; support development of preclinical laboratories to advance gene therapies; Determine the high-resolution molecular structures for several of the HIV proteins and apply these structures to the rational design of drugs as part of the targeted drug development program; determine generalizable and effective approaches for the use of macromolecular structure in designing drugs to combat HIV infection and AIDS; make resolved structures available in publicly accessible data bases;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics	Improve screening, discovery, and preclinical development of therapeutic agents that demonstrate activity against retroviruses, fostering activity by and in collaboration with industry (continued)	Increase understanding of the mechanisms and limitations of drug resistance; study the effect of various agents on HIV replication and viral variation; evaluate early markers of resistance; evaluate the activity of anti-HIV drugs in various cell types (including macrophages) and in various stages of the cell cycle; and Develop new compounds capable of inhibiting the sexual transmission of HIV, such as topical microbicides (which may inhibit HIV and STDs associated with enhanced HIV transmission), HIV-specific viricides, and systemic agents.					
Therapeutics	Perform clinical trials of agents active against HIV based on an understanding of pathogenesis with emphasis on improved design and methodologies, and integrate clinical trials with ongoing natural history studies	Support and improve clinical trials of potential therapeutic agents and combinations of agents in studies to determine pharmacokinetics and bioavailability and evaluate anti-HIV combinations that are non-cross-resistant, synergistic, and toxicity-sparing and that may delay development of drug-resistant HIV strains; enhance collaboration between and within ICDs to facilitate opportunities for clinical trials; Increase the understanding of the pathogenesis of HIV disease based on the evaluation of antiretroviral agents in clinical trials;	145,105	151,627	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics	Perform clinical trials of agents active against HIV based on an understanding of pathogenesis with emphasis on improved design and methodologies, and integrate clinical trials with ongoing natural history studies (continued)	Implement the development and evaluation of virologic, immunologic, and clinical markers to assess drug activity and determine the prognostic value of these markers in response to therapeutic interventions; Support research and development of clinical trials methodology and study design so that appropriate pathways are taken rapidly to evaluate the activity, clinical efficacy, and the ultimate acceptability of new agents and approaches that translate into clinical use; Improve the utilization of GCRCs for the conduct of single and multi-institutional clinical trials; Establish and expand appropriate career training programs for laboratory investigators, clinical investigators, and translational scientists; Develop and validate quality-of-life parameters included in patient assessments of clinical trials; Support research on the effectiveness of pharmacologic (including compliance with therapies and STD prevention) and non-pharmacologic (including psychosocial) interventions (including nutritional factors and adherence improvement);					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics	Perform clinical trials of agents active against HIV based on an understanding of pathogenesis with emphasis on improved design and methodologies, and integrate clinical trials with ongoing natural history studies (continued)	Investigate possible interactions between therapies for HIV-related disease and other substances that HIV-infected individuals might use, such as drug abuse treatment medications, oral contraceptives or other prescription drugs, nonprescription drugs, alternative or complementary therapies, or drugs of abuse; Coordinate studies to encourage co-enrollment of patients on all trials where appropriate (co-enrollment would not only allow for better utilization of limited resources but also enable assessment of concomitant medications and their interactions, improving the efficiency of the primary study); Develop a coordinated plan to evaluate long-term therapeutic strategies, e.g., develop plans for long-term followup, enroll patients in sequential randomized trials once they have reached an end point in their initial trial; and Evaluate new and existing compounds capable of inhibiting the sexual transmission of HIV, such as topical microbicides and HIV-specific viricides; nested studies to evaluate the infectivity of body fluids, such as semen and cervical secretions in trials of antiretroviral therapies.					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics	Extend our understanding of immunopathogenesis through the development and testing of strategies that enhance and/or restore the deficient immune systems of HIV-infected individuals	Evaluate therapeutic approaches that test specific hypotheses of HIV immunopathogenesis; Develop and validate new methods to evaluate immune function in the context of clinical trials; Continue and accelerate the testing of cytokines and modulators of cytokines either alone or in combination with antiretroviral agents for the purpose of reconstituting the deficient immune systems of HIV-infected individuals; Develop and evaluate various approaches of active and passive immunotherapy for both HIV infection and its sequelae; Develop a program of reconstituting the immune systems of HIV-infected individuals by administration of cellular elements in an autologous, syngeneic, or allogeneic fashion, including use of expanded peripheral blood T cells, bone marrow transplantation, thymic transplantation, cord blood, stem cells, and/or xenogeneic transplantation;	18,619	19,349	All populations		
Therapeutics	Extend our understanding of immunopathogenesis through the development and testing of strategies that enhance and/or restore the deficient immune systems of HIV-infected individuals (continued)	Develop new therapeutic strategies based on gene therapy approaches to protect or potentially reconstitute the immune system;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
		Use structural biologic techniques to determine the structures of various cytokines and cytokine receptors as potential targets for HIV therapies; and Enhance collaboration among ICDs to facilitate the conduct of immune-based therapeutic trials and to enhance pathogenesis-related research in HIV-infected individuals.					
Therapeutics	Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs and other infections modified by HIV infection, including those specific to women, children, and drug users	Support basic research on OIs in order to increase fundamental knowledge and to identify new therapeutic targets and strategies and understand how pathogens contribute to morbidity, such as wasting syndrome. Determine the high-resolution molecular structures for OI proteins and apply these structures to the rational design of drugs as part of the targeted drug development program and determine generalizable and effective approaches for the use of macromolecular structure in designing drugs to combat OIs associated with AIDS;	107,915	111,887	All populations		
Therapeutics	Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs and other infections modified by HIV infection, including those specific to women, children, and drug users (continued)	Support discovery and preclinical programs to develop therapies especially targeting cryptosporidia, microsporidia, JC virus, CMV, HPV, and azole-resistant fungal organisms, with emphasis on bioavailable agents with favorable pharmacokinetics. Develop <i>in vitro</i> culture systems for OIs such as <i>Pneumocystis carinii</i> ;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics		Further conduct clinical trials for the prophylaxis and treatment of HIV-associated OIs in HIV-infected individuals, including pregnant women and children and drug users. Important OIs include <i>Mycobacterium tuberculosis</i> infection (TB), <i>Mycobacterium avium</i> complex, cytomegalovirus infection, cryptosporidiosis, microsporidiosis, cryptococcal disease, azole-resistant fungal infection, toxoplasmosis, PCP, acyclovir-resistant herpes infections, progressive multifocal leukoencephalopathy (PML), bacterial infections, and other infections whose course is affected by HIV. Evaluate immune-based therapies as adjuncts for treating OIs;					
	Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs and other infections modified by HIV infection, including those specific to women, children, and drug users (continued)	Determine the optimal strategies and combinations of agents to prevent and treat multiple OIs (i.e., multiple opportunistic pathogen prophylaxis studies [MOPPS]), and their effects in combination with antiretroviral agents. Strategies need to focus on time of initiation, compliance, pharmacologic interactions, toxicities and adverse reactions (e.g., trimethoprim sulfamethoxazole reactions), and minimizing development of resistance; studies should include quality-of-life assessments and cost-benefit analyses;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics	Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs and other infections modified by HIV infection, including those specific to women, children, and drug users (continued)	Develop and utilize animal models for preclinical efficacy and safety testing of potential agents for OIs, including mutagenicity and teratogenicity; Develop clinically useful assays for the rapid diagnosis, treatment response, and sensitivity testing of OIs, especially TB, MAI, enterics, CMV, HSV, fungi, toxoplasma, and JC virus; Support training of basic investigators, clinical investigators, and translational investigators for OI research; and					
		Determine the role and capability of preexisting immunity (both induced and natural) to control OI infections and the ability of HIV-infected individuals to respond to vaccination throughout the course of infection and disease.					
Therapeutics	Accelerate the development, evaluation, and implementation of strategies to interrupt vertical transmission of HIV from mother to child	Support the rapid translation of basic research observations to strategies for the interruption of vertical transmission; apply the results of clinical trials to the investigation of pathogenesis and to clinical practice;	5,690	6,138	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics	Accelerate the development, evaluation, and implementation of strategies to interrupt vertical transmission of HIV from mother to child (continued)	Develop strategies and agents to interrupt the vertical transmission of HIV from pregnant women to their offspring, including antiviral agents, anti-HIV immunoglobulin, and monoclonal antibodies, HIV vaccines, adjuvants, virucides, and other intrapartum interventions; explore the potential of combined strategies; evaluate the safety, toxicity, pharmacokinetics, and antiretroviral activity of anti-HIV agents in pregnant women and newborns;					
		Expand the obstetrical and pediatric infrastructure for the conduct of perinatal trials through collaborative efforts, both national and international;					
		Support the long-term followup of all women and children who participate in perinatal trials to evaluate potential distant effects of antiretroviral agents and/or biologicals;					
		Investigate the role of the placenta in transmission of anti-HIV drugs from mother to fetus;					
		Develop and improve sensitive and specific diagnostic parameters that are cost-effective to permit early differentiation of HIV-infection status in children born to HIV-infected mothers;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
		Assess the potential efficacy and feasibility of obstetric interventions to prevent vertical transmissions, such as cesarean deliveries and other aspects of intrapartum care; Evaluate the risk of vertical transmission of drug-resistant virus; and Evaluate factors that contribute to or protect against vertical transmission; develop effective strategies that could more easily be afforded globally to help reduce vertical transmission and perhaps decrease transmission via breast milk.					
Therapeutics	Target the discovery, development, and clinical evaluation of improved therapeutic strategies for the treatment and prevention of HIV-associated malignancies based on an understanding of pathogenesis	Support basic research on HIV-associated malignancies to increase fundamental knowledge of the etiology, pathogenesis, and biology of these neoplasms; develop preclinical models for testing potential therapeutic strategies; Identify novel mechanisms and targets (e.g., cytokines, angiogenesis, viral or hormonal cofactors) for treatment and prevention of HIV-associated tumors, including Kaposi's sarcoma, non-Hodgkin's lymphoma, HPV-associated malignancies, and others, and develop new therapeutic strategies on the basis of these findings;	16,642	16,939	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics	Target the discovery, development, and clinical evaluation of improved therapeutic strategies for the treatment and prevention of HIV-associated malignancies based on an understanding of pathogenesis (continued)	Use structural biologic and biochemical information to rationally design drugs to inhibit specific pathogenic factors of HIV-associated malignancies (e.g., oncoprotein of HPV);					
		Encourage the development and coordinate the conduct of clinical trials that concurrently evaluate therapeutic strategies directed against the malignancy with anti-retroviral and anti-OI strategies in order to assess the effects of such treatment on the malignancy as well as on the underlying HIV infection, immune function, and clinical course;					
		Continue and expand screening, discovery, and development of novel therapeutic agents with activity against HIV-associated malignancies (e.g., agents with better CNS penetration, agents with better safety profiles);					
		Develop trials to optimize existing therapies for malignancies in HIV-infected patients, including therapeutic adjuncts such as hematopoietic colony-stimulating factors and supportive care; develop and validate quality-of-life assessments;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
		Encourage collaborative studies to develop mechanisms for early identification of patients at high risk for malignancy and to develop and assess interventional strategies to reduce or prevent the development of malignancies; Support training of basic investigators, clinical investigators, and translational scientists for research of malignancies in HIV-infected patients; Improve diagnostic methods for early diagnosis of malignancies and for early detection of recurrent cancer; Coordinate referral of patients with malignancy end points on other studies to malignancy trials; and					
Therapeutics	Target the discovery, development, and clinical evaluation of improved therapeutic strategies for the treatment and prevention of HIV-associated malignancies based on an understanding of pathogenesis (continued)	Improve collaboration between various adult and pediatric cooperative groups conducting clinical trials of HIV-associated malignancies and ICDs and industry to accelerate trials completion and approval of active agents.					
Therapeutics	Develop an understanding of the neuropathogenesis of HIV infection and strategies for assessing, preventing, and treating neurologic disease in the course of HIV infection	Develop an improved understanding of the biology and epidemiology of neurologic disease in HIV-infected individuals;	11,614	12,268	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Therapeutics	Develop an understanding of the neuropathogenesis of HIV infection and strategies for assessing, preventing, and treating neurologic disease in the course of HIV infection (continued)	Develop novel strategies and agents that are active against putative pathways of HIV-induced CNS dysfunction, e.g., inhibitors of quinolinic acid, excitatory neurotransmitters, gp160/120, and other potential neurotoxins;					
		Implement studies related to the delineation of mechanisms responsible for impaired neurocognitive development in children born to HIV-infected mothers, and develop strategies directed at the prevention and treatment of this complication of HIV infection;					
		Implement clinical trials addressing nervous system complications of HIV infection and incorporate neurologic assessments into other HIV-related clinical trials;					
		Develop therapeutic agents that are capable of crossing the blood-brain barrier and are active against HIV infection in relevant cells in the CNS; develop an understanding of mechanisms involved in penetration of the blood-brain barrier;					
		Better delineate etiologies of peripheral neuropathy in HIV infection, and develop strategies to prevent and treat this complication;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
		Develop and utilize <i>in vitro</i> and animal models of CNS impairment and ADC to further identify agents that can reverse HIV neuropathogenesis; and Implement assessments and approaches for the diagnosis of HIV-related dementia in clinical studies; implement standardized adult and pediatric neuropsychologic and neurologic assessment batteries in clinical studies and evaluate treatment-induced changes in neurocognitive impairment in a linguistically and culturally sensitive context.					
Therapeutics	Develop therapies for the treatment and prevention of serious HIV-associated complications, including wasting syndrome, growth failure, metabolic disorders, dermatologic disorders, ITP, nephropathy, oral diseases, and other symptoms and serious complications	Support research into the biology of the various clinical sequelae of HIV infection (above); Develop and evaluate therapeutic strategies to ameliorate the various sequelae of HIV infection (above) based on an increased understanding of pathogenesis; Develop and evaluate therapeutic strategies for alleviating the various symptoms of unclear etiology in HIV-infected persons (above) and improving the quality of life; and Develop and validate quality-of-life parameters for the various sequelae of HIV infection (above).	12,844	15,431	All populations		

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

(Dollars in thousands)

Therapeutics

FY 1994 Estimate	FY 1995 Estimate	FY 1996 By-pass
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Objective 1	Improve screening, discovery, and preclinical development of therapeutic agents that demonstrate activity against retroviruses, fostering activity by and in collaboration with industry.	\$105,268	\$113,086	\$134,980
Objective 2	Perform clinical trials of agents active against HIV based on an understanding of pathogenesis with emphasis on improved design and methodologies, and integrate clinical trials with ongoing natural history studies.	197,114	204,982	216,181
Objective 3	Extend our understanding of immunopathogenesis through the development and testing of strategies that enhance and/or restore the deficient immune systems of HIV-infected individuals.	17,084	18,300	21,779
Objective 4	Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs and other infections modified by HIV infection, including those specific to women, children, and drug users.	72,578	77,561	97,787
Objective 5	Accelerate the development, evaluation, and implementation of strategies to interrupt vertical transmission of HIV from mother to child.	29,227	29,854	29,474
Objective 6	Target the discovery, development, and clinical evaluation of improved therapeutic strategies for the treatment and prevention of HIV-associated malignancies based on an understanding of pathogenesis.	16,385	16,394	17,430
Objective 7	Develop an understanding of the neuropathogenesis of HIV infection and strategies for assessing, preventing, and treating neurologic disease in the course of HIV infection.	10,858	11,179	11,658
Objective 8	Develop therapies for the treatment and prevention of serious HIV-associated complications, including wasting syndrome, growth failure, metabolic disorders, dermatologic disorders, ITP, nephropathy, oral diseases, and other symptoms and serious complications.	9,932	11,479	16,116

TOTAL, Therapeutics	458,446	482,835	545,405
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FY96 Plan

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

(Dollars in thousands)

Therapeutics

FY 1994 Actual	FY 1995 Appropriation	FY 1996 Pres. Bud.
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Objective 1	Improve screening, discovery, and preclinical development of therapeutic agents that demonstrate activity against retroviruses, fostering activity by and in collaboration with industry.	\$150,382	\$154,833	\$162,200
Objective 2	Perform clinical trials of agents active against HIV based on an understanding of pathogenesis with emphasis on improved design and methodologies, and integrate clinical trials with ongoing natural history studies.	138,440	145,105	151,627
Objective 3	Extend our understanding of immunopathogenesis through the development and testing of strategies that enhance and/or restore the deficient immune systems of HIV-infected individuals.	17,892	18,619	19,349
Objective 4	Target the discovery, development, and evaluation of potential agents for prevention and treatment of HIV-associated OIs and other infections modified by HIV infection, including those specific to women, children, and drug users.	104,670	107,915	111,887
Objective 5	Accelerate the development, evaluation, and implementation of strategies to interrupt vertical transmission of HIV from mother to child.	5,621	5,690	6,138
Objective 6	Target the discovery, development, and clinical evaluation of improved therapeutic strategies for the treatment and prevention of HIV-associated malignancies based on an understanding of pathogenesis.	15,788	16,642	16,939
Objective 7	Develop an understanding of the neuropathogenesis of HIV infection and strategies for assessing, preventing, and treating neurologic disease in the course of HIV infection.	11,506	11,614	12,268
Objective 8	Develop therapies for the treatment and prevention of serious HIV-associated complications, including wasting syndrome, growth failure, metabolic disorders, dermatologic disorders, ITP, nephropathy, oral diseases, and other symptoms and serious complications.	11,777	12,844	15,431

TOTAL, Therapeutics	456,076	473,262	495,839
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RESEARCH

Agency: National Institutes of Health

Goal: ^{Improve understanding of} ~~Conduct and support research on~~ the natural history and epidemiology of HIV infection and AIDS in all populations

Objective: ^① ~~Natural History and Epidemiology~~ ^{Collect natural history and epi. data to further understanding of HIV transmission and progression.}

Action Steps: Develop and assess intervention strategies to reduce or prevent HIV transmission

Descriptions: Support development and evaluation of improved, acceptable, effective physical and non-irritating chemical barrier methods and conduct research on existing barrier methods to prevent sexual transmission of HIV and STDs;

assist in the development of P.A.T.I.X. interventions

Develop strategies and conduct studies to evaluate vaccines, drugs, and other interventions such as cesarean sections, vaginal cleansing, and breast-feeding practices that prevent perinatal transmission. ~~These should include randomized trials where possible, cooperation between study groups, and re-analysis of data from existing studies, where appropriate;~~

Assess the efficacy of combined strategies that decrease blood-borne transmission of HIV; for example, evaluating existing needle exchange programs, the use of bleach as a disinfectant, and drug abuse prevention and treatment on reducing HIV transmission and seroincidence;

SAME AS STRATEGY

Develop domestic and international cohort-based infrastructures for testing HIV vaccines and other interventions (e.g., microbicides, behavioral) for preventing HIV transmission;

Develop and evaluate interventions related to sexual behavior, including (1) STD treatment and prevention and their effects on HIV transmission, (2) interventions focused on influencing safe sexual behaviors, reproductive decision-making, and contraceptive choices for women, and (3) integration of health care delivery systems such as those that combine reproductive health and STD/HIV prevention and treatment services;

Develop methods of outreach that would engage high-risk populations, enroll them in research to identify factors that contribute to high-risk behavior, and increase and maintain compliance with interventions as well as recruit and retain hard-to-reach populations in studies;

Incorporate interdisciplinary evaluation research designs of HIV prevention strategies to ensure adequacy of findings

regarding outcome, process, and descriptive analysis;

Evaluate the social acceptability, the ease of compliance, and barriers to access and use of interventions (e.g., AZT for perinatal transmission, virucides);

Develop and evaluate improved procedures for screening, monitoring, and inactivating HIV and other retroviruses in the blood supply; and develop and evaluate alternatives to allogeneic blood transfusion, including artificial blood substitutes and hematopoietic growth factors; and

Assess the impact of drug and alcohol abuse on efficacy of behavior modification interventions directed at sexual transmission.

CONSOLIDATED
FY 95: 48,656

FY 96: 48,137

Populations Served: All populations

Constituency Involvement:

Unmet Need:

Examine the role of risk factors and mechanisms of HIV transmission to assist in the development of biologically- and behaviorally-based interventions.

Objective: ~~Natural History and Epidemiology~~

②
Action Steps: Characterize the risk factors and mechanisms of HIV transmission in various populations

Descriptions: Evaluate HIV transmission in relationship to:

- AME
- a. viral factors, virus load in the blood and at mucosal sites, characteristics of the HIV virus present (virus subtype and phenotype), and co-infection with other viruses (HTLV and HIV2);
 - b. host factors such as pregnancy, menstrual cycle, hormonal contraceptives, and HLA type;
 - c. local factors including intercurrent STDs, oral and anogenital inflammation (ulceration), mucosal immunity, and anatomic factors such as ectopy; and
 - d. behavioral risk factors, such as (oral and anal sex;) *questioned*

Further differentiate the timing and mechanism of perinatal transmission;

Study susceptibility to HIV infection, especially in individuals who are at high risk for repeated exposure to HIV but who remain uninfected, in order to determine factors related to resistance, including mucosal immunity, viral, genetic, and other immunologic factors, endocrinologic factors, and other factors;

Determine the role of breast-feeding in the transmission of HIV from infected mother to child; and

Examine the extent to which drug use (including alcohol and tobacco) and drug-using behaviors affect susceptibility and/or transmission of HIV.

FY 95: 24,271

FY 96: 26,257

CONSIDER DRAFTED
Populations Served: All populations

Constituency Involvement:

Unmet Need:

Enhance understanding of HIV-related disease progression
to assist in the development of effective treatment strategies for
HIV-infected patients.

Objective: ~~Natural History and Epidemiology~~

③

Action Steps: Elucidate the progression of HIV-related disease, from early infection through long-term consequences and sequelae, with the goal of understanding, preventing, and treating those factors that may lead to disease

Descriptions: Identify pathogenic mechanisms and cofactors for disease progression and disease-specific outcomes in well-defined subsets of individuals (e.g., high-CD4 long-term survivors, low-CD4 long-term survivors, rapid progressors). Studies should include investigation of behavioral, genetic, virologic, immunologic, and host factors;

In diverse populations, describe the full spectrum of HIV-related disease, including OIs, HIV-related malignancies, wasting, and organ-specific complications; evaluate the impact of sociodemographic variables, gender, age, and route of transmission on HIV disease progression, time to AIDS, and specific outcomes;

Study the natural history of early HIV infection;

Evaluate issues specific to HIV-infected children, including: (1) mechanisms that contribute to impaired growth and neurodevelopment, (2) impact on childhood infectious diseases and the safety and efficacy of immunization, and (3) childhood-specific complications including lymphoid interstitial pneumonitis;

Evaluate the interaction of hormonal factors (including pregnancy, contraceptives, and hormonal replacement therapy) and HIV disease progression;

Maintain longitudinal cohorts and create linkage with clinical studies (e.g., ACTG, CPCRA) to (1) efficiently examine the full spectrum of disease, (2) assess the impact of therapies on the frequency and severity of HIV-related sequelae, disease progression, and survival, and (3) assess and validate laboratory and behavioral markers;

Study the progression of HIV-related disease in adolescents ~~who have acquired their diseases as a result of injecting drug use and/or sexual activity;~~

Study the factors that predict, protect against, contribute to, or limit the progression of HIV infection in the nervous system including early cognitive impairment, dementia, and neuropathy;

Develop, maintain, and expand national repositories for the collection and banking of blood, other body fluids, and tissue specimens obtained from longitudinal cohort studies

SAME

and other well-characterized populations of HIV-infected individuals as a resource for studies of HIV-mediated pathogenesis, correlates of immunity to HIV infection, and specific HIV-related outcomes;

Study the nutritional and absorption factors that predict, protect against, contribute to, or limit the progression of HIV-related wasting and weight loss;

Evaluate strategies of care delivery and case management to determine their impact on HIV disease progression and quality of life;

Elucidate the mechanisms of HIV-associated carcinogenesis and improve strategies for early diagnosis and for effectively treating these malignancies;

Study oral lesions in HIV disease and progression; and

Study the long-term natural history of related retroviruses (e.g., HTLV and HIV-2) to elucidate retroviral pathogenesis and resistance mechanisms.

FY 95: 53,565

FY 96: 59,574

Populations Served: All populations

Constituency Involvement:

Unmet Need:

	95	96	Bypass
#1	48,656	48,137	73,066
#2	24,271	26,257	52,624
#3	53,565	59,574	54,883
#4	23,074	23,210	28,395
#5	29,448	31,644	(28,303) lower
	188,822	237,271	Δ 48,449

Enhance understanding of susceptibility to HIV infection.

Objective: ⁽⁴⁾ ~~Natural History and Epidemiology~~

Action Steps: Identify, ^{questioned} evaluate, and apply innovative laboratory and ~~behavioral~~ strategies to study epidemiologically defined populations with regard to transmission and progression of HIV disease

Descriptions: Apply cutting-edge laboratory approaches and behavioral strategies to assess susceptibility to infection and transmission and monitor disease progression and response to intervention in population studies;

Facilitate the transfer of novel laboratory and behavioral strategies from basic research to epidemiologic applications;

Promote development and application of laboratory approaches to elucidate mechanisms, cofactors, and timing of maternal-fetal-infant transmission of HIV infection;

Assess new virologic parameters (e.g., viral burden, genotype/phenotype) applicable to body fluids that correlate with infectiousness for evaluating interventions (e.g., spermicides/microbicides, vaccines);

Identify laboratory parameters associated with HIV-related outcomes, such as intermediate end points preceding HIV-associated infections and malignancies, predictors of long-term survival or rapid progression, and markers of exposure to HIV without infection;

Facilitate, develop, evaluate, and apply assays for assessment of mucosal immunity related to susceptibility to infection and impact of intervention;

Identify, characterize, and evaluate reliable diagnostic markers, including markers in saliva, for the purpose of applying rapid and sensitive diagnostic technologies for detecting HIV infection;

Promote development and assessment of assays to detect HIV infection in vaccinated populations; and

Establish, maintain, and expand national repositories of biologic specimens (e.g., blood, body fluid, and tissue) obtained from well-characterized individuals in longitudinal studies to facilitate rapid evaluation of existing strategies and development of new strategies.

FY 95: 23,074

FY 96: 23,210

Populations Served: All populations

Constituency Involvement:

Unmet Need:

Enhance understanding of HIV disease in populations
in which HIV is prevalent, emerging, and/or increasing
for the purpose of developing treatments and preventive
vaccines.

⑤ **Objective:** ~~Natural History and Epidemiology~~

Action Steps: Perform the epidemiologic studies of HIV infection, related conditions, and risk behaviors in domestic and international populations in which HIV is prevalent, emerging, and/or increasing

Descriptions: Identify emerging high-risk groups in the United States through seroincidence studies and identification of behavior risk factors in the population. Examples of groups that need particular attention and further evaluation include minorities, women, adolescents, children, young gay men, homeless mentally ill, drug users, and the incarcerated;

Develop infrastructure to define populations in the United States and throughout the world with high incidence and prevalence suitable for vaccine and other intervention trials;

Delineate the epidemiology of behavioral risk factors for HIV in defined population-based studies;

Measure the occurrence of other infectious agents, e.g., other viruses (HTLV-1, HSV-2, hepatitis B and C, etc.), sexually transmitted diseases, and mycobacterium (e.g., MTB, *M. avium*) in populations at risk for HIV;

Coordinate with the CDC, WHO, and other institutions to maintain a comprehensive view of the epidemic with as much detailed information about subpopulations as possible;

Promote the development of new high-quality biometry programs for AIDS research evaluation, including new methodologies;

Define the scope and role of HIV in the etiology of cancer and determine the impact of HIV-related malignancy on total cancer burden in the population; and

Cooperate with health services agencies to determine why many individuals and groups continue to underutilize health services related to HIV that are already available (e.g., access to care, perceptions regarding efficacy, etc.).

FY 95: 29,448

FY 96: 31,644

Populations Served: All populations

Constituency Involvement:

Unmet Need:

c:\work\wp\wp51\wp\data\nihcpi.cwa

179,014

188,822

Bypass

In strategy,

RESEARCH

Agency: National Institutes of Health

Goal: Improve understanding of the natural history and epidemiology of HIV infection and AIDS in all populations.

Objective 1: Collect natural history and epidemiological data to further understanding of HIV transmission and progression.

Action Steps: Develop and assess intervention strategies to assist in the development of treatment and prevention interventions.

Descriptions: Support development and evaluation of improved, acceptable, effective physical and non-irritating chemical barrier methods and conduct research on existing barrier methods to prevent sexual transmission of HIV and STDs;

Develop strategies and conduct studies to evaluate vaccines, drugs, and other interventions such as cesarean sections, vaginal cleansing, and breast-feeding practices that prevent perinatal transmission;

Assess the efficacy of combined strategies that decrease blood-borne transmission of HIV; for example, evaluating existing needle exchange programs, the use of bleach as a disinfectant, and drug abuse prevention and treatment on reducing HIV transmission and seroincidence;

Develop domestic and international cohort-based infrastructures for testing HIV vaccines and other interventions (e.g., microbicides, behavioral) for preventing HIV transmission;

Develop and evaluate interventions related to sexual behavior, including (1) STD treatment and prevention and their effects on HIV transmission, (2) interventions focused on influencing safe sexual behaviors, reproductive decision-making, and contraceptive choices for women, and (3) integration of health care delivery systems such as those that combine reproductive health and STD/HIV prevention and treatment services;

Develop methods of outreach that would engage high-risk populations, enroll them in research to identify factors that contribute to high-risk behavior, and increase and maintain compliance with interventions as well as recruit and retain hard-to-reach populations in studies;

Incorporate interdisciplinary evaluation research designs of HIV prevention strategies to ensure adequacy of findings

regarding outcome, process, and descriptive analysis;

Evaluate the social acceptability, the ease of compliance, and barriers to access and use of interventions (e.g., AZT for perinatal transmission, virucides);

Develop and evaluate improved procedures for screening, monitoring, and inactivating HIV and other retroviruses in the blood supply; and develop and evaluate alternatives to allogeneic blood transfusion, including artificial blood substitutes and hematopoietic growth factors; and

Assess the impact of drug and alcohol abuse on efficacy of behavior modification interventions directed at sexual transmission.

Objective 2: Examine the role of risk factors and mechanisms of HIV transmission to assist in the development of biologically- and behaviorally-based interventions.

Action Steps: Characterize the risk factors and mechanisms of HIV transmission in various populations.

Descriptions: Evaluate HIV transmission in relationship to:

- a. viral factors, virus load in the blood and at mucosal sites, characteristics of the HIV virus present (virus subtype and phenotype), and co-infection with other viruses (HTLV and HIV2);
- b. host factors such as pregnancy, menstrual cycle, hormonal contraceptives, and HLA type;
- c. local factors including intercurrent STDs, oral and anogenital inflammation (ulceration), mucosal immunity, and anatomic factors such as ectopy; and
- d. behavioral risk factors, such as oral and anal sex;

Further differentiate the timing and mechanism of perinatal transmission;

Study susceptibility to HIV infection, especially in individuals who are at high risk for repeated exposure to HIV but who remain uninfected, in order to determine factors related to resistance, including mucosal immunity, viral, genetic, and other immunologic factors, endocrinologic factors, and other factors;

Determine the role of breast-feeding in the transmission of HIV from infected mother to child; and

Examine the extent to which drug use (including alcohol and tobacco) and drug-using behaviors affect susceptibility and/or transmission of HIV.

Objective 3: Enhance understanding of HIV-related disease progression to assist in the development of effective treatment strategies for HIV-infected patients.

Action Steps: Elucidate the progression of HIV-related disease, from early infection through long-term consequences and sequelae, with the goal of understanding, preventing, and treating those factors that may lead to disease

Descriptions: Identify pathogenic mechanisms and cofactors for disease progression and disease-specific outcomes in well-defined subsets of individuals (e.g., high-CD4 long-term survivors, low-CD4 long-term survivors, rapid progressors). Studies should include investigation of behavioral, genetic, virologic, immunologic, and host factors;

In diverse populations, describe the full spectrum of HIV-related disease, including OIs, HIV-related malignancies, wasting, and organ-specific complications; evaluate the impact of sociodemographic variables, gender, age, and route of transmission on HIV disease progression, time to AIDS, and specific outcomes;

Study the natural history of early HIV infection;

Evaluate issues specific to HIV-infected children, including: (1) mechanisms that contribute to impaired growth and neurodevelopment, (2) impact on childhood infectious diseases and the safety and efficacy of immunization, and (3) childhood-specific complications including lymphoid interstitial pneumonitis;

Evaluate the interaction of hormonal factors (including pregnancy, contraceptives, and hormonal replacement therapy) and HIV disease progression;

Maintain longitudinal cohorts and create linkage with clinical studies (e.g., ACTG, CPCRA) to (1) efficiently examine the full spectrum of disease, (2) assess the impact of therapies on the frequency and severity of HIV-related sequelae, disease progression, and survival, and (3) assess and validate laboratory and behavioral markers;

Study the progression of HIV-related disease in adolescents;

Study the factors that predict, protect against, contribute to, or limit the progression of HIV infection in the nervous system including early cognitive impairment, dementia, and neuropathy;

Develop, maintain, and expand national repositories for the collection and banking of blood, other body fluids, and

tissue specimens obtained from longitudinal cohort studies and other well-characterized populations of HIV-infected individuals as a resource for studies of HIV-mediated pathogenesis, correlates of immunity to HIV infection, and specific HIV-related outcomes;

Study the nutritional and absorption factors that predict, protect against, contribute to, or limit the progression of HIV-related wasting and weight loss;

Evaluate strategies of care delivery and case management to determine their impact on HIV disease progression and quality of life;

Elucidate the mechanisms of HIV-associated carcinogenesis and improve strategies for early diagnosis and for effectively treating these malignancies;

Study oral lesions in HIV disease and progression; and

Study the long-term natural history of related retroviruses (e.g., HTLV and HIV-2) to elucidate retroviral pathogenesis and resistance mechanisms.

Objective 4: Enhance understanding of susceptibility to HIV infection.

Action Steps: Identify, evaluate, and apply innovative laboratory and behavioral strategies to study epidemiologically defined populations with regard to transmission and progression of HIV disease.

Descriptions: Apply cutting-edge laboratory approaches and behavioral strategies to assess susceptibility to infection and transmission and monitor disease progression and response to intervention in population studies;

Facilitate the transfer of novel laboratory and behavioral strategies from basic research to epidemiologic applications;

Promote development and application of laboratory approaches to elucidate mechanisms, cofactors, and timing of maternal-fetal-infant transmission of HIV infection;

Assess new virologic parameters (e.g., viral burden, genotype/phenotype) applicable to body fluids that correlate with infectiousness for evaluating interventions (e.g., spermicides/microbicides, vaccines);

Identify laboratory parameters associated with HIV-related outcomes, such as intermediate end points preceding HIV-associated infections and malignancies, predictors of long-term survival or rapid progression, and markers of exposure to HIV without infection;

Facilitate, develop, evaluate, and apply assays for assessment of mucosal immunity related to susceptibility to infection and impact of intervention;

Identify, characterize, and evaluate reliable diagnostic markers, including markers in saliva, for the purpose of applying rapid and sensitive diagnostic technologies for detecting HIV infection;

Promote development and assessment of assays to detect HIV infection in vaccinated populations; and

Establish, maintain, and expand national repositories of biologic specimens (e.g., blood, body fluid, and tissue) obtained from well-characterized individuals in longitudinal studies to facilitate rapid evaluation of existing strategies and development of new strategies.

5/
Objective 4: Enhance understanding of HIV disease in populations in which HIV is prevalent, emerging, and/or increasing for the purpose of developing treatments and preventive vaccines.

Action Steps: Perform the epidemiologic studies of HIV infection, related conditions, and risk behaviors in domestic and international populations in which HIV is prevalent, emerging, and/or increasing.

Descriptions: Identify emerging high-risk groups in the United States through seroincidence studies and identification of behavior risk factors in the population. Examples of groups that need particular attention and further evaluation include minorities, women, adolescents, children, young gay men, homeless mentally ill, drug users, and the incarcerated;

Develop infrastructure to define populations in the United States and throughout the world with high incidence and prevalence suitable for vaccine and other intervention trials;

Delineate the epidemiology of behavioral risk factors for HIV in defined population-based studies;

Measure the occurrence of other infectious agents, e.g., other viruses (HTLV-1, HSV-2, hepatitis B and C, etc.), sexually transmitted diseases, and mycobacterium (e.g., MTB, *M. avium*) in populations at risk for HIV;

Coordinate with the CDC, WHO, and other institutions to maintain a comprehensive view of the epidemic with as much detailed information about subpopulations as possible;

Promote the development of new high-quality biometry programs for AIDS research evaluation, including new methodologies;

Define the scope and role of HIV in the etiology of cancer and determine the impact of HIV-related malignancy on total cancer burden in the population; and

Cooperate with health services agencies to determine why many individuals and groups continue to underutilize health services related to HIV that are already available (e.g., access to care, perceptions regarding efficacy, etc.).

FY 95: 179,014

FY 96: 188,822

Pops. Served: All populations

Constituency Involvement: Researchers, clinicians, community and patient representatives, NIAID Advisory Council, ARAC, and OAR

Advisory Committees. Others?

Unmet Needs: The NIH FY 1996 Plan and Budget Estimate for Scientific Opportunities in HIV-Related Research identified areas for further productive research in this area in the amount of \$48,449 over the FY 96 figure.

National Institutes of Health

Area Research

Goal 1 Conduct and support research on the natural history and epidemiology of HIV infection and AIDS in all populations

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Develop and assess intervention strategies to reduce or prevent HIV transmission	Support development and evaluation of improved, acceptable, effective physical and non-irritating chemical barrier methods and conduct research on existing barrier methods to prevent sexual transmission of HIV and STDs; Develop strategies and conduct studies to evaluate vaccines, drugs, and other interventions such as cesarean sections, vaginal cleansing, and breast-feeding practices that prevent perinatal transmission. These should include randomized trials where possible, cooperation between study groups, and re-analysis of data from existing studies, where appropriate; Assess the efficacy of combined strategies that decrease blood-borne transmission of HIV; for example, evaluating existing needle exchange programs, the use of bleach as a disinfectant, and drug abuse prevention and treatment on reducing HIV transmission and seroincidence;	48,656	48,137	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Develop and assess intervention strategies to reduce or prevent HIV transmission (continued)	Develop domestic and international cohort-based infrastructures for testing HIV vaccines and other interventions (e.g., microbicides, behavioral) for preventing HIV transmission; Develop and evaluate interventions related to sexual behavior, including (1) STD treatment and prevention and their effects on HIV transmission, (2) interventions focused on influencing safe sexual behaviors, reproductive decision-making, and contraceptive choices for women, and (3) integration of health care delivery systems such as those that combine reproductive health and STD/HIV prevention and treatment services; Develop methods of outreach that would engage high-risk populations, enroll them in research to identify factors that contribute to high-risk behavior, and increase and maintain compliance with interventions as well as recruit and retain hard-to-reach populations in studies; Incorporate interdisciplinary evaluation research designs of HIV prevention strategies to ensure adequacy of findings regarding outcome, process, and descriptive analysis;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Develop and assess intervention strategies to reduce or prevent HIV transmission (continued)	Evaluate the social acceptability, the ease of compliance, and barriers to access and use of interventions (e.g., AZT for perinatal transmission, virucides); Develop and evaluate improved procedures for screening, monitoring, and inactivating HIV and other retroviruses in the blood supply; and develop and evaluate alternatives to allogeneic blood transfusion, including artificial blood substitutes and hematopoietic growth factors; and Assess the impact of drug and alcohol abuse on efficacy of behavior modification interventions directed at sexual transmission.					
Natural History and Epidemiology	Characterize the risk factors and mechanisms of HIV transmission in various populations	Evaluate HIV transmission in relationship to: a. viral factors, virus load in the blood and at mucosal sites, characteristics of the HIV virus present (virus subtype and phenotype), and co-infection with other viruses (HTLV and HIV2); b. host factors such as pregnancy, menstrual cycle, hormonal contraceptives, and HLA type;	24,271	26,257	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Characterize the risk factors and mechanisms of HIV transmission in various populations (continued)	c. local factors including intercurrent STDs, oral and anogenital inflammation (ulceration), mucosal immunity, and anatomic factors such as ectopy; and d. behavioral risk factors, such as oral and anal sex; Further differentiate the timing and mechanism of perinatal transmission; Study susceptibility to HIV infection, especially in individuals who are at high risk for repeated exposure to HIV but who remain uninfected, in order to determine factors related to resistance, including mucosal immunity, viral, genetic, and other immunologic factors, endocrinologic factors, and other factors; Determine the role of breast-feeding in the transmission of HIV from infected mother to child; and Examine the extent to which drug use (including alcohol and tobacco) and drug-using behaviors affect susceptibility and/or transmission of HIV.					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Elucidate the progression of HIV-related disease, from early infection through long-term consequences and sequelae, with the goal of understanding, preventing, and treating those factors that may lead to disease	Identify pathogenic mechanisms and cofactors for disease progression and disease-specific outcomes in well-defined subsets of individuals (e.g., high-CD4 long-term survivors, low-CD4 long-term survivors, rapid progressors). Studies should include investigation of behavioral, genetic, virologic, immunologic, and host factors; In diverse populations, describe the full spectrum of HIV-related disease, including OIs, HIV-related malignancies, wasting, and organ-specific complications; evaluate the impact of sociodemographic variables, gender, age, and route of transmission on HIV disease progression, time to AIDS, and specific outcomes; Study the natural history of early HIV infection; Evaluate issues specific to HIV-infected children, including: (1) mechanisms that contribute to impaired growth and neurodevelopment, (2) impact on childhood infectious diseases and the safety and efficacy of immunization, and (3) childhood-specific complications including lymphoid interstitial pneumonitis;	53,565	59,574	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Elucidate the progression of HIV-related disease, from early infection through long-term consequences and sequelae, with the goal of understanding, preventing, and treating those factors that may lead to disease (continued)	Evaluate the interaction of hormonal factors (including pregnancy, contraceptives, and hormonal replacement therapy) and HIV disease progression; Maintain longitudinal cohorts and create linkage with clinical studies (e.g., ACTG, CPCRA) to (1) efficiently examine the full spectrum of disease, (2) assess the impact of therapies on the frequency and severity of HIV-related sequelae, disease progression, and survival, and (3) assess and validate laboratory and behavioral markers; Study the progression of HIV-related disease in adolescents who have acquired their diseases as a result of injecting drug use and/or sexual activity; Study the factors that predict, protect against, contribute to, or limit the progression of HIV infection in the nervous system including early cognitive impairment, dementia, and neuropathy;					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Elucidate the progression of HIV-related disease, from early infection through long-term consequences and sequelae, with the goal of understanding, preventing, and treating those factors that may lead to disease (continued)	Develop, maintain, and expand national repositories for the collection and banking of blood, other body fluids, and tissue specimens obtained from longitudinal cohort studies and other well-characterized populations of HIV-infected individuals as a resource for studies of HIV-mediated pathogenesis, correlates of immunity to HIV infection, and specific HIV-related outcomes; Study the nutritional and absorption factors that predict, protect against, contribute to, or limit the progression of HIV-related wasting and weight loss; Evaluate strategies of care delivery and case management to determine their impact on HIV disease progression and quality of life; Elucidate the mechanisms of HIV-associated carcinogenesis and improve strategies for early diagnosis and for effectively treating these malignancies; Study oral lesions in HIV disease and progression; and Study the long-term natural history of related retroviruses (e.g., HTLV and HIV-2) to elucidate retroviral pathogenesis and resistance mechanisms.					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Identify, evaluate, and apply innovative laboratory and behavioral strategies to study epidemiologically defined populations with regard to transmission and progression of HIV disease	Apply cutting-edge laboratory approaches and behavioral strategies to assess susceptibility to infection and transmission and monitor disease progression and response to intervention in population studies; Facilitate the transfer of novel laboratory and behavioral strategies from basic research to epidemiologic applications; Promote development and application of laboratory approaches to elucidate mechanisms, cofactors, and timing of maternal-fetal-infant transmission of HIV infection; Assess new virologic parameters (e.g., viral burden, genotype/phenotype) applicable to body fluids that correlate with infectiousness for evaluating interventions (e.g., spermicides/microbicides, vaccines); Identify laboratory parameters associated with HIV-related outcomes, such as intermediate end points preceding HIV-associated infections and malignancies, predictors of long-term survival or rapid progression, and markers of exposure to HIV without infection;	23,074	23,210	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Identify, evaluate, and apply innovative laboratory and behavioral strategies to study epidemiologically defined populations with regard to transmission and progression of HIV disease (continued)	Facilitate, develop, evaluate, and apply assays for assessment of mucosal immunity related to susceptibility to infection and impact of intervention; Identify, characterize, and evaluate reliable diagnostic markers, including markers in saliva, for the purpose of applying rapid and sensitive diagnostic technologies for detecting HIV infection; Promote development and assessment of assays to detect HIV infection in vaccinated populations; and Establish, maintain, and expand national repositories of biologic specimens (e.g., blood, body fluid, and tissue) obtained from well-characterized individuals in longitudinal studies to facilitate rapid evaluation of existing strategies and development of new strategies.					

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Perform the epidemiologic studies of HIV infection, related conditions, and risk behaviors in domestic and international populations in which HIV is prevalent, emerging, and/or increasing	Identify emerging high-risk groups in the United States through seroincidence studies and identification of behavior risk factors in the population. Examples of groups that need particular attention and further evaluation include minorities, women, adolescents, children, young gay men, homeless mentally ill, drug users, and the incarcerated; Develop infrastructure to define populations in the United States and throughout the world with high incidence and prevalence suitable for vaccine and other intervention trials; Delineate the epidemiology of behavioral risk factors for HIV in defined population-based studies; Measure the occurrence of other infectious agents, e.g., other viruses (HTLV-1, HSV-2, hepatitis B and C, etc.), sexually transmitted diseases, and mycobacterium (e.g., MTB, <i>M. avium</i>) in populations at risk for HIV; Coordinate with the CDC, WHO, and other institutions to maintain a comprehensive view of the epidemic with as much detailed information about subpopulations as possible;	29,448	31,644	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Natural History and Epidemiology	Perform the epidemiologic studies of HIV infection, related conditions, and risk behaviors in domestic and international populations in which HIV is prevalent, emerging, and/or increasing (continued)	Promote the development of new high-quality biometry programs for AIDS research evaluation, including new methodologies; Define the scope and role of HIV in the etiology of cancer and determine the impact of HIV-related malignancy on total cancer burden in the population; and Cooperate with health services agencies to determine why many individuals and groups continue to underutilize health services related to HIV that are already available (e.g., access to care, perceptions regarding efficacy, etc.).					

CWA v. CWB = CWC

RESEARCH

Agency: National Institutes of Health

Goal: Improve understanding of the natural history and epidemiology of HIV infection and AIDS in all populations.

Objective 1: Collect natural history and epidemiological data to further understanding of HIV transmission and progression.

Action Steps: Develop and assess intervention strategies to assist in the development of treatment and prevention interventions.

~~Conduct and support research on the natural history and epidemiology of HIV infection and AIDS in all populations~~

Objective: Natural History and Epidemiology

~~**Action Steps:** Develop and assess intervention strategies to reduce or prevent HIV transmission~~

Descriptions: Support development and evaluation of improved, acceptable, effective physical and non-irritating chemical barrier methods and conduct research on existing barrier methods to prevent sexual transmission of HIV and STDs;

Develop strategies and conduct studies to evaluate vaccines, drugs, and other interventions such as cesarean sections, vaginal cleansing, and breast-feeding practices that prevent perinatal transmission; and breast-feeding practices that prevent perinatal transmission. These should include randomized trials where possible, cooperation between study groups, and re-analysis of data from existing studies, where appropriate;

Assess the efficacy of combined strategies that decrease blood-borne transmission of HIV; for example, evaluating existing needle exchange programs, the use of bleach as a disinfectant, and drug abuse prevention and treatment on reducing HIV transmission and seroincidence;

Develop domestic and international cohort-based infrastructures for testing HIV vaccines and other interventions (e.g., microbicides, behavioral) for preventing HIV transmission;

Develop and evaluate interventions related to sexual behavior, including (1) STD treatment and prevention and their effects on HIV transmission, (2) interventions focused on influencing safe sexual behaviors, reproductive decision-making, and contraceptive choices for women, and (3) integration of health care delivery systems such as those

that combine reproductive health and STD/HIV prevention and treatment services;

Develop methods of outreach that would engage high-risk populations, enroll them in research to identify factors that contribute to high-risk behavior, and increase and maintain compliance with interventions as well as recruit and retain hard-to-reach populations in studies;

Incorporate interdisciplinary evaluation research designs of HIV prevention strategies to ensure adequacy of findings regarding outcome, process, and descriptive analysis;

Evaluate the social acceptability, the ease of compliance, and barriers to access and use of interventions (e.g., AZT for perinatal transmission, virucides);

Develop and evaluate improved procedures for screening, monitoring, and inactivating HIV and other retroviruses in the blood supply; and develop and evaluate alternatives to allogeneic blood transfusion, including artificial blood substitutes and hematopoietic growth factors; and

Assess the impact of drug and alcohol abuse on efficacy of behavior modification interventions directed at sexual transmission.

Objective 2: Examine the role of risk factors and mechanisms of HIV transmission to assist in the development of biologically- and behaviorally-based interventions.

Action Steps: Characterize the risk factors and mechanisms of HIV transmission in various populations.

~~FY 95: 48,656~~

~~FY 96: 48,137~~

~~Populations Served: All populations~~

~~Constituency Involvement:~~

~~Unmet Need:~~

~~Objective: Natural History and Epidemiology~~

~~Action Steps:~~ Characterize the risk factors and mechanisms of HIV transmission in various populations

Descriptions: Evaluate HIV transmission in relationship to:

- a. viral factors, virus load in the blood and at mucosal sites, characteristics of the HIV virus present (virus subtype and phenotype), and co-infection with other viruses (HTLV and HIV2);
- b. host factors such as pregnancy, menstrual cycle, hormonal contraceptives, and HLA type;
- c. local factors including intercurrent STDs, oral and anogenital inflammation (ulceration), mucosal immunity, and anatomic factors such as ectopy; and
- d. behavioral risk factors, such as oral and anal sex;

Further differentiate the timing and mechanism of perinatal transmission;

Study susceptibility to HIV infection, especially in individuals who are at high risk for repeated exposure to HIV but who remain uninfected, in order to determine factors related to resistance, including mucosal immunity, viral, genetic, and other immunologic factors, endocrinologic factors, and other factors;

Determine the role of breast-feeding in the transmission of HIV from infected mother to child; and

Examine the extent to which drug use (including alcohol and tobacco) and drug-using behaviors affect susceptibility and/or transmission of HIV.

Objective 3: Enhance understanding of HIV-related disease progression to assist in the development of effective treatment strategies for HIV-infected patients.

~~FY 95: 24,271~~

~~FY 96: 26,257~~

~~Populations Served:~~ All populations

~~Constituency Involvement:~~

~~Unmet Need:~~

~~Objective: Natural History and Epidemiology~~

Action Steps: Elucidate the progression of HIV-related disease, from early infection through long-term consequences and sequelae, with the goal of understanding, preventing, and treating those factors that may lead to disease

Descriptions: Identify pathogenic mechanisms and cofactors for disease progression and disease-specific outcomes in well-defined subsets of individuals (e.g., high-CD4 long-term survivors, low-CD4 long-term survivors, rapid progressors). Studies should include investigation of behavioral, genetic, virologic, immunologic, and host factors;

In diverse populations, describe the full spectrum of HIV-related disease, including OIs, HIV-related malignancies, wasting, and organ-specific complications; evaluate the impact of sociodemographic variables, gender, age, and route of transmission on HIV disease progression, time to AIDS, and specific outcomes;

Study the natural history of early HIV infection;

Evaluate issues specific to HIV-infected children, including: (1) mechanisms that contribute to impaired growth and neurodevelopment, (2) impact on childhood infectious diseases and the safety and efficacy of immunization, and (3) childhood-specific complications including lymphoid interstitial pneumonitis;

Evaluate the interaction of hormonal factors (including pregnancy, contraceptives, and hormonal replacement therapy) and HIV disease progression;

Maintain longitudinal cohorts and create linkage with clinical studies (e.g., ACTG, CPCRA) to (1) efficiently examine the full spectrum of disease, (2) assess the impact of therapies on the frequency and severity of HIV-related sequelae, disease progression, and survival, and (3) assess and validate laboratory and behavioral markers;

~~Study the progression of HIV-related disease in adolescents;
Study the progression of HIV-related disease in adolescents who have acquired their diseases as a result of injecting drug use and/or sexual activity;~~

Study the factors that predict, protect against, contribute to, or limit the progression of HIV infection in the nervous system including early cognitive impairment, dementia, and neuropathy;

Develop, maintain, and expand national repositories for the

collection and banking of blood, other body fluids, and tissue specimens obtained from longitudinal cohort studies and other well-characterized populations of HIV-infected individuals as a resource for studies of HIV-mediated pathogenesis, correlates of immunity to HIV infection, and specific HIV-related outcomes;

Study the nutritional and absorption factors that predict, protect against, contribute to, or limit the progression of HIV-related wasting and weight loss;

Evaluate strategies of care delivery and case management to determine their impact on HIV disease progression and quality of life;

Elucidate the mechanisms of HIV-associated carcinogenesis and improve strategies for early diagnosis and for effectively treating these malignancies;

Study oral lesions in HIV disease and progression; and

Study the long-term natural history of related retroviruses (e.g., HTLV and HIV-2) to elucidate retroviral pathogenesis and resistance mechanisms.

Objective 4: Enhance understanding of susceptibility to HIV infection.

FY 95: 53,565

FY 96: 59,574

~~Populations Served: All populations~~

~~Constituency Involvement:~~

~~Unmet Need:~~

Objective: Natural History and Epidemiology

Action Steps: Identify, evaluate, and apply innovative laboratory and behavioral strategies to study epidemiologically defined populations with regard to transmission and progression of HIV disease.

~~and apply innovative laboratory and behavioral strategies to study epidemiologically defined populations with regard to transmission and progression of HIV disease~~

Descriptions: Apply cutting-edge laboratory approaches and behavioral strategies to assess susceptibility to infection and transmission and monitor disease progression and response to intervention in population studies;

Facilitate the transfer of novel laboratory and behavioral strategies from basic research to epidemiologic applications;

Promote development and application of laboratory approaches to elucidate mechanisms, cofactors, and timing of maternal-fetal-infant transmission of HIV infection;

Assess new virologic parameters (e.g., viral burden, genotype/phenotype) applicable to body fluids that correlate with infectiousness for evaluating interventions (e.g., spermicides/microbicides, vaccines);

Identify laboratory parameters associated with HIV-related outcomes, such as intermediate end points preceding HIV-associated infections and malignancies, predictors of long-term survival or rapid progression, and markers of exposure to HIV without infection;

Facilitate, develop, evaluate, and apply assays for assessment of mucosal immunity related to susceptibility to infection and impact of intervention;

Identify, characterize, and evaluate reliable diagnostic markers, including markers in saliva, for the purpose of applying rapid and sensitive diagnostic technologies for detecting HIV infection;

Promote development and assessment of assays to detect HIV infection in vaccinated populations; and

Establish, maintain, and expand national repositories of biologic specimens (e.g., blood, body fluid, and tissue) obtained from well-characterized individuals in longitudinal studies to facilitate rapid evaluation of existing strategies and development of new strategies.

Objective 4: Enhance understanding of HIV disease in populations in which HIV is prevalent, emerging, and/or increasing for the

purpose of developing treatments and preventive vaccines.

~~FY 95: 23,074~~

~~FY 96: 23,210~~

~~Populations Served: All populations~~

~~Constituency Involvement: Constituency Involvement:—~~

~~Unmet Need:—~~

Objective: ~~Natural History and Epidemiology~~

Action Steps: Perform the epidemiologic studies of HIV infection, related conditions, and risk behaviors in domestic and international populations in which HIV is prevalent, emerging, ~~and/or increasing.~~
~~and/or increasing~~

Descriptions: Identify emerging high-risk groups in the United States through ~~seroincidence studies~~ and identification of behavior risk factors in the population. Examples of groups that need particular attention and further evaluation include minorities, women, adolescents, children, young gay men, homeless mentally ill, drug users, and the incarcerated;

Develop infrastructure to define populations in the United States and throughout the world with high incidence and prevalence suitable for vaccine and other intervention trials;

Delineate the epidemiology of behavioral risk factors for HIV in defined population-based studies;

Measure the occurrence of other infectious agents, e.g., other viruses (HTLV-1, HSV-2, hepatitis B and C, etc.), sexually transmitted diseases, and mycobacterium (e.g., MTB, *M. avium*) in populations at risk for HIV;

Coordinate with the CDC, WHO, and other institutions to maintain a comprehensive view of the epidemic with as much detailed information about subpopulations as possible;

Promote the development of new high-quality biometry programs for AIDS research evaluation, including new methodologies;

Define the scope and role of HIV in the etiology of cancer and determine the impact of HIV-related malignancy on total cancer burden in the population; and

~~Cooperate with health services agencies to determine why many individuals and groups continue to underutilize health services related to HIV that are already available (e.g., access to care, perceptions regarding efficacy, etc.).~~

FY 95: 179,014

FY 96: 188,822

Pops. Served: All populations

Constituency Involvement: Researchers, clinicians, community and patient representatives, NIAID Advisory Council, ARAC, and OAR Advisory Committees. Others?

Unmet Needs: The NIH FY 1996 Plan and Budget Estimate for Scientific Opportunities in HIV-Related Research identified areas for further productive research in this area in the amount of \$48,449 over the FY 96 figure.

~~-29,448~~

~~FY 96: 31,644~~

~~**Populations Served:** All populations~~

~~**Constituency Involvement:**~~

~~**Unmet Need:**~~

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FY96
Bypass

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

(Dollars in thousands)

Natural History and Epidemiology:

		FY 1994 Estimate	FY 1995 Estimate	FY 1996 By-pass
Objective 1	Develop and assess intervention strategies to reduce or prevent HIV transmission.	\$51,754	\$58,141	\$73,066
Objective 2	Characterize the risk factors and mechanisms of HIV transmission in various populations.	44,078	47,218	52,624
Objective 3	Elucidate the progression of HIV-related disease, from early infection through long-term consequences and sequelae, with the goal of understanding, preventing, and treating those factors that may lead to disease.	47,809	50,031	54,883
Objective 4	Identify, evaluate, and apply innovative laboratory and behavioral strategies to study epidemiologically defined populations with regard to transmission and progression of HIV disease.	24,080	24,706	28,395
Objective 5	Perform the epidemiologic studies of HIV infection, related conditions, and risk behaviors in domestic and international populations in which HIV is prevalent, emerging, and/or increasing.	23,656	25,594	28,303
TOTAL, Natural History and Epidemiology		191,377	205,690	237,271

FY 96 Plan

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

(Dollars in thousands)

Natural History and Epidemiology:

		FY 1994 Actual	FY 1995 Appropriation	FY 1996 Pres. Bud.
Objective 1	Develop and assess intervention strategies to reduce or prevent HIV transmission.	\$39,045	\$48,656	\$48,137
Objective 2	Characterize the risk factors and mechanisms of HIV transmission in various populations.	22,506	24,271	26,257
Objective 3	Elucidate the progression of HIV-related disease, from early infection through long-term consequences and sequelae, with the goal of understanding, preventing, and treating those factors that may lead to disease.	60,945	53,565	59,574
Objective 4	Identify, evaluate, and apply innovative laboratory and behavioral strategies to study epidemiologically defined populations with regard to transmission and progression of HIV disease.	22,681	23,074	23,210
Objective 5	Perform the epidemiologic studies of HIV infection, related conditions, and risk behaviors in domestic and international populations in which HIV is prevalent, emerging, and/or increasing.	30,825	29,448	31,644
TOTAL, Natural History and Epidemiology		176,002	179,014	188,822

In Strategy

Etiol/Path

RESEARCH

Agency: National Institutes of Health

Goal: Enhance understanding of the etiology and pathogenesis of HIV infection.

Objective 1: Support research to further understanding of HIV immunopathogenesis.

Action Steps: Delineate the cellular and molecular mechanisms associated with viral immunopathogenesis.

Descriptions: Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of target cells/tissues;

Define the virologic (load and phenotype), immunologic (specific and nonspecific), genetic, and environmental factors that contribute to disease progression and nonprogression;

Delineate the molecular mechanisms by which virus-derived factors regulate HIV replication and pathogenesis, with special emphasis on the use of primary virus isolates and cells;

Delineate the role of immune activation and host factors, including cytokines, in HIV replication and pathogenesis;

Delineate the role of lymphoid organs, including mucosal-associated lymphoid tissue, in HIV pathogenesis;

Further develop and utilize experimental models to examine the pathogenesis of lentiviral infections;

Delineate the role of lymphoid and hematopoietic precursor cells and their microenvironment in immune impairment;

Develop new assay systems for effective measurement of changes in viral load and host immune function that are predictive of disease progression;

Delineate the range of cell types infected by HIV *in vivo* and their potential role as viral reservoirs; and

Establish and expand collaborative programs to facilitate sharing of key patient samples, animal model resources, and laboratory reagents.

Objective 2: Support research to enhance understanding of HIV-related immune dysfunction.

Action Steps: Delineate the molecular and cellular mechanisms of transmission and establishment of infection and their impact on disease progression.

Descriptions: Define the cellular and immune mechanisms that inhibit/enhance the early events in establishing HIV infection;

Determine the impact of early events in the establishment of HIV infection on the clinical course of disease;

Determine the cell or tissue type that serves as the portal of entry of HIV and the impact of STDs and other pathogenic processes that influence HIV transmission;

Determine the effects of viral genotype and load on transmission of cell-free and cell-associated virus;

Determine the roles of specific and nonspecific mucosal immunity and host factors that inhibit/enhance HIV transmission;

Determine the mechanisms of vertical HIV transmission; and

Elucidate unique aspects of HIV transmission and disease progression in underresearched populations.

Objective 3: Support research to enhance understanding of HIV-related malignancies.

Action Steps: Elucidate the etiologic factors and cofactors in the pathogenesis of HIV-related malignancies.

Descriptions: Elucidate the role of HIV infection, immune dysfunction, and interactions with potential cofactors in the development of HIV-associated malignancies;

Identify the characteristics of the host that predispose to development of malignant disease, including genetic, hormonal, growth factor, cytokine, and immunologic characteristics; and

Identify the molecular correlates of HIV-associated malignancies, including but not limited to oncogenes, tumor suppressor genes, tumor promoters and carcinogens, and viral and microbial genes and proteins.

Objective 4: Support research to enhance understanding of HIV-related neuropathogenesis.

Action Steps: Elucidate the pathogenic mechanisms involved

in HIV-associated neurological diseases.

Descriptions: Investigate the contributions of viral infection and virally induced indirect factors (in neuronal and non-neuronal cells) to nervous system impairment;

Delineate how HIV enters and persists in the nervous system and causes functional impairment;

Investigate both biological and environmental factors that may affect nervous system function in the context of HIV disease;

Study the effects of neurotrophins and immunoregulatory and proinflammatory cytokines on both host and viral gene expression;

Delineate the role of OIs and drug treatment in neurologic complications of AIDS, including peripheral neuropathies, hearing and visual loss, and behavioral changes;

Assess neural tissue and organs as virus reservoirs in HIV disease and as sources of specifically neurovirulent/neuroinvasive viral strains; and

Develop neuroimaging tools for correlative structural-functional studies of progressive HIV-associated neurological disorders.

Objective 5: Support research to enhance understanding of HIV-related opportunistic infections.

Action Steps: Elucidate the pathogenesis of HIV-related opportunistic infections.

Descriptions: Investigate the mechanisms of immune function that mediate protection against the OIs;

Develop *in vitro* techniques and animal models, where needed, to propagate the opportunistic micro-organisms and conduct studies designed to provide details of the basic biology and pathogenic mechanisms of these micro-organisms;

Identify and elucidate the genetic and environmental risk factors associated with susceptibility, development, and progression of opportunistic infections;

Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated opportunistic infections;

Study the effects of OIs on immune dysfunction; and

Elucidate immunologic markers that are correlative with

disease progression for HIV-associated OIs and develop assays to accurately monitor these markers as a function of therapy.

Objective 6: Support research to enhance understanding of HIV-related wasting syndrome.

Action Steps: Elucidate the etiology and pathophysiology of HIV-related wasting, failure to thrive, and growth retardation.

Descriptions: Define alterations in body composition, nutritional status, metabolic patterns, energy balance, and growth and development associated with HIV infection; and

Elucidate the pathogenesis of HIV-associated wasting and impaired growth and development, including the roles of cytokines, malabsorption, anorexia, opportunistic infections, HIV, and other factors.

Objective 7: Support research to enhance understanding of HIV-related organ and tissue disorders.

Action Steps: Elucidate the etiology and pathogenesis of HIV-related organ/tissue-specific disorders, such as HIV-associated renal, gastrointestinal, endocrine, cardiopulmonary, autoimmune, and other diseases

Descriptions: Investigate the etiologic and pathogenic mechanisms of HIV-associated enteropathy, including the role of HIV, opportunistic infections, tumors, and other factors;

Identify host, viral, environmental, and other factors responsible for the pathogenesis and progression of HIV-associated nephropathy;

Elucidate the etiology and pathogenesis of endocrine dysfunction and the role of alteration in the endocrine/immune axis in progression of HIV disease; and

Elucidate the etiology and pathogenesis of HIV-related cardiopulmonary disease and other organ/tissue-specific manifestations, including autoimmune disease.

FY 95: 345,663

FY 96: 374,767

Pops. Served: All populations

Constituency Involvement: Researchers, clinicians, community and patient representatives, NIAID Advisory Council, ARAC, and OAR Advisory Committees. Others?

Unmet Needs: The NIH FY 1996 Plan and Budget Estimate for Scientific Opportunities in HIV-Related Research identified areas for further productive research in this area in the amount of \$46,216 over the FY 96 figure.

RESEARCH

Agency: National Institutes of Health

Goal: ^{Enhance understanding of} ~~Conduct and support research on the etiology and pathogenesis of HIV infection, to define the mechanism by which the virus causes disease~~

Objective: ^① ~~Etiology and Pathogenesis~~ ^{Support Research to further understanding of HIV immuno-pathogenesis.}

Action Steps: Delineate the cellular and molecular mechanisms associated with the viral immunopathogenesis of ~~HIV-related immune dysfunction~~

Descriptions: Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of target cells/tissues;

Define the virologic (load and phenotype), immunologic (specific and nonspecific), genetic, and environmental factors that contribute to disease progression and nonprogression;

SAME
Delineate the molecular mechanisms by which virus-derived factors regulate HIV replication and pathogenesis, with special emphasis on the use of primary virus isolates and cells;

Delineate the role of immune activation and host factors, including cytokines, in HIV replication and pathogenesis;

Delineate the role of lymphoid organs, including mucosal-associated lymphoid tissue, in HIV pathogenesis;

Further develop and utilize experimental models to examine the pathogenesis of lentiviral infections;

Delineate the role of lymphoid and hematopoietic precursor cells and their microenvironment in immune impairment;

Develop new assay systems for effective measurement of changes in viral load and host immune function that are predictive of disease progression;

Delineate the range of cell types infected by HIV *in vivo* and their potential role as viral reservoirs; and

Establish and expand collaborative programs to facilitate sharing of key patient samples, animal model resources, and laboratory reagents.

FY 95: 201,040

FY 96: 217,368

contest,
Populations Served: All populations

Constituency Involvement:

Unmet Need:

②
Objective: ~~Etiology and Pathogenesis~~ *Support Research to enhance understanding of HIV-related immune dysfunction.*

Action Steps: Delineate the molecular and cellular mechanisms of transmission and establishment of infection and their impact on disease progression

Descriptions: Define the cellular and immune mechanisms that inhibit/enhance the early events in establishing HIV infection;

Determine the impact of early events in the establishment of HIV infection on the clinical course of disease;

Determine the cell or tissue type that serves as the portal of entry of HIV and the impact of STDs and other pathogenic processes that influence HIV transmission;

Determine the effects of viral genotype and load on transmission of cell-free and cell-associated virus;

Determine the roles of specific and nonspecific mucosal immunity and host factors that inhibit/enhance HIV transmission;

Determine the mechanisms of vertical HIV transmission; and

Elucidate unique aspects of HIV transmission and disease progression in underresearched populations.

FY 95: 28,140

FY 96: 34,233

questioned

Populations Served: All populations

Constituency Involvement:

Unmet Need:

SAME

Consolidated

③ *Support research enhance understanding of HIV-related malignancies*
Objective: ~~Etiology and Pathogenesis~~ *malignancies,*

Action Steps: Elucidate the etiologic factors and cofactors in the pathogenesis of HIV-related malignancies

Descriptions: Elucidate the role of HIV infection, immune dysfunction, and interactions with potential cofactors in the development of HIV-associated malignancies;

same
Identify the characteristics of the host that predispose to development of malignant disease, including genetic, hormonal, growth factor, cytokine, and immunologic characteristics; and

Identify the molecular correlates of HIV-associated malignancies, including but not limited to oncogenes, tumor suppressor genes, tumor promoters and carcinogens, and viral and microbial genes and proteins.

FY 95: 28,544

FY 96: 28,941

Populations Served: All populations

Constituency Involvement:

Unmet Need:

④ Support research to enhance understanding of HIV-related neuropathogenesis.
Objective: Etiology and Pathogenesis

Action Steps: Elucidate the pathogenic mechanisms involved in HIV-associated neurological diseases

Descriptions: Investigate the contributions of viral infection and virally induced indirect factors (in neuronal and non-neuronal cells) to nervous system impairment;

Delineate how HIV enters and persists in the nervous system and causes functional impairment;

Investigate both biological and environmental factors that may affect nervous system function in the context of HIV disease, ~~using neurological and appropriate neuropsychologic assessment tools;~~

Study the effects of neurotrophins and immunoregulatory and proinflammatory cytokines on both host and viral gene expression;

Delineate the role of OIs and drug treatment in neurologic complications of AIDS, including peripheral neuropathies, hearing and visual loss, and behavioral changes;

Assess neural tissue and organs as virus reservoirs in HIV disease and as sources of specifically neurovirulent/neuroinvasive viral strains; and

Develop neuroimaging tools for correlative structural-functional studies of progressive HIV-associated neurological disorders.

FY 95: 38,984

FY 96: 41,067

Populations Served: All populations

Constituency Involvement:

Unmet Need:

⑤ Support research to enhance understanding of HIV-related OIs, -
Objective: Etiology and Pathogenesis

Action Steps: Elucidate the pathogenesis of HIV-related opportunistic infections

Descriptions: Elucidate the mechanisms of immune function that mediate protection against the OIs;

Develop *in vitro* techniques and animal models, where needed, to propagate the opportunistic micro-organisms and conduct studies designed to provide details of the basic biology and pathogenic mechanisms of these micro-organisms;

Identify and elucidate the genetic and environmental risk factors associated with susceptibility, development, and progression of opportunistic infections;

Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated opportunistic infections;

Study the effects of OIs on immune dysfunction; and

Elucidate immunologic markers that are correlative with disease progression for HIV-associated OIs and develop assays to accurately monitor these markers as a function of therapy.

FY 95: 32,222

FY 96: 35,151

Populations Served: All populations

Constituency Involvement:

Unmet Need:

SAME

⑥ Support research to enhance understanding of HIV-related wasting syndrome.
Objective: ~~Etiology and Pathogenesis~~

Action Steps: Elucidate the etiology and pathophysiology of HIV-related wasting, failure to thrive, and growth retardation

Descriptions: Define alterations in body composition, nutritional status, metabolic patterns, energy balance, and growth and development associated with HIV infection; and

Elucidate the pathogenesis of HIV-associated wasting and impaired growth and development, including the roles of cytokines, malabsorption, anorexia, opportunistic infections, HIV, and other factors.

FY 95: 2,931

FY 96: 2,918

Populations Served: All populations

Constituent Involvement:

Unmet Need:

⑦ *Support Research to enhance understanding of HIV-related*
Objective: ~~Etiology and Pathogenesis~~ *Organ + Tissue disorders,*

Action Steps: Elucidate the etiology and pathogenesis of HIV-related organ/tissue-specific disorders, such as HIV-associated renal, gastrointestinal, endocrine, cardiopulmonary, autoimmune, and other diseases

Descriptions: Investigate the etiologic and pathogenic mechanisms of HIV-associated enteropathy, including the role of HIV, opportunistic infections, tumors, and other factors;

Shine
Identify host, viral, environmental, and other factors responsible for the pathogenesis and progression of HIV-associated nephropathy;

Elucidate the etiology and pathogenesis of endocrine dysfunction and the role of alteration in the endocrine/immune axis in progression of HIV disease; and

Elucidate the etiology and pathogenesis of HIV-related cardiopulmonary disease and other organ/tissue-specific manifestations, including autoimmune disease.

FY 95: 13,802

FY 96: 15,089

Populations Served: All populations

Constituency Involvement:

Unmet Need:

	95	96	Bypass
#1	201,040	217,368	168,661
2	28,140	34,233	114,152
3 Sa	28,544	28,941	16,795
4 Sb	38,984	41,067	47,363
5 Sc	32,222	35,151	48,775
6 Sd	2,931	2918	6,638
7 Se	13,802	15,089	18,599

374,767 420,983 Δ 46,216

Area Research

Goal 2 Conduct and support research on the etiology and pathogenesis of HIV infection to define the mechanism by which the virus causes disease

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Etiology and Pathogenesis	Delineate the cellular and molecular mechanisms associated with the viral immunopathogenesis of HIV-related immune dysfunction	Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of target cells/tissues;	201,040	217,368	All populations		
		Define the virologic (load and phenotype), immunologic (specific and nonspecific), genetic, and environmental factors that contribute to disease progression and nonprogression;					
		Delineate the molecular mechanisms by which virus-derived factors regulate HIV replication and pathogenesis, with special emphasis on the use of primary virus isolates and cells;					
		Delineate the role of immune activation and host factors, including cytokines, in HIV replication and pathogenesis;					
		Delineate the role of lymphoid organs, including mucosal-associated lymphoid tissue, in HIV pathogenesis;					
		Further develop and utilize experimental models to examine the pathogenesis of lentiviral infections;					
		Delineate the role of lymphoid and hematopoietic precursor cells and their microenvironment in immune impairment;					

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Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Etiology and Pathogenesis	Delineate the cellular and molecular mechanisms associated with the viral immunopathogenesis of HIV-related immune dysfunction (continued)	Develop new assay systems for effective measurement of changes in viral load and host immune function that are predictive of disease progression; Delineate the range of cell types infected by HIV <i>in vivo</i> and their potential role as viral reservoirs; and Establish and expand collaborative programs to facilitate sharing of key patient samples, animal model resources, and laboratory reagents.					
Etiology and Pathogenesis	Delineate the molecular and cellular mechanisms of transmission and establishment of infection and their impact on disease progression	Define the cellular and immune mechanisms that inhibit/enhance the early events in establishing HIV infection; Determine the impact of early events in the establishment of HIV infection on the clinical course of disease; Determine the cell or tissue type that serves as the portal of entry of HIV and the impact of STDs and other pathogenic processes that influence HIV transmission; Determine the effects of viral genotype and load on transmission of cell-free and cell-associated virus;	28,140	34,233	All populations		
Etiology and Pathogenesis	Delineate the molecular and cellular mechanisms of transmission and establishment of infection and their impact on disease progression (continued)	Determine the roles of specific and nonspecific mucosal immunity and host factors that inhibit/enhance HIV transmission; Determine the mechanisms of vertical HIV transmission; and					

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Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
		Elucidate unique aspects of HIV transmission and disease progression in underresearched populations.					
Etiology and Pathogenesis	Elucidate the etiologic factors and cofactors in the pathogenesis of HIV-related malignancies	Elucidate the role of HIV infection, immune dysfunction, and interactions with potential cofactors in the development of HIV-associated malignancies; Identify the characteristics of the host that predispose to development of malignant disease, including genetic, hormonal, growth factor, cytokine, and immunologic characteristics; and Identify the molecular correlates of HIV-associated malignancies, including but not limited to oncogenes, tumor suppressor genes, tumor promoters and carcinogens, and viral and microbial genes and proteins.	28,544	28,941	All populations		

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Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Etiology and Pathogenesis	Elucidate the pathogenic mechanisms involved in HIV-associated neurological diseases	Investigate the contributions of viral infection and virally induced indirect factors (in neuronal and non-neuronal cells) to nervous system impairment; Delineate how HIV enters and persists in the nervous system and causes functional impairment; Investigate both biological and environmental factors that may affect nervous system function in the context of HIV disease, using neurological and appropriate neuropsychologic assessment tools; Study the effects of neurotrophins and immunoregulatory and proinflammatory cytokines on both host and viral gene expression; Delineate the role of OIs and drug treatment in neurologic complications of AIDS, including peripheral neuropathies, hearing and visual loss, and behavioral changes; Assess neural tissue and organs as virus reservoirs in HIV disease and as sources of specifically neurovirulent/neuroinvasive viral strains; and Develop neuroimaging tools for correlative structural-functional studies of progressive HIV-associated neurological disorders.	38,984	41,067	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Etiology and Pathogenesis	Elucidate the pathogenesis of HIV-related opportunistic infections	Elucidate the mechanisms of immune function that mediate protection against the OIs; Develop <i>in vitro</i> techniques and animal models, where needed, to propagate the opportunistic micro-organisms and conduct studies designed to provide details of the basic biology and pathogenic mechanisms of these micro-organisms; Identify and elucidate the genetic and environmental risk factors associated with susceptibility, development, and progression of opportunistic infections; Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated opportunistic infections; Study the effects of OIs on immune dysfunction; and Elucidate immunologic markers that are correlative with disease progression for HIV-associated OIs and develop assays to accurately monitor these markers as a function of therapy.	32,222	35,151	All populations		

Objectives	Action Steps	Programs					
		Descriptions	Resources in Thousands		Populations Served	Constituency Involvement	Unmet Needs
			FY 1995 (appropri.)	FY 1996 (proposed)			
Etiology and Pathogenesis	Elucidate the etiology and pathophysiology of HIV-related wasting, failure to thrive, and growth retardation	Define alterations in body composition, nutritional status, metabolic patterns, energy balance, and growth and development associated with HIV infection; and Elucidate the pathogenesis of HIV-associated wasting and impaired growth and development, including the roles of cytokines, malabsorption, anorexia, opportunistic infections, HIV, and other factors.	2,931	2,918	All populations		
Etiology and Pathogenesis	Elucidate the etiology and pathogenesis of HIV-related organ/tissue-specific disorders, such as HIV-associated renal, gastrointestinal, endocrine, cardiopulmonary, autoimmune, and other diseases	Investigate the etiologic and pathogenic mechanisms of HIV-associated enteropathy, including the role of HIV, opportunistic infections, tumors, and other factors; Identify host, viral, environmental, and other factors responsible for the pathogenesis and progression of HIV-associated nephropathy; Elucidate the etiology and pathogenesis of endocrine dysfunction and the role of alteration in the endocrine/immune axis in progression of HIV disease; and Elucidate the etiology and pathogenesis of HIV-related cardiopulmonary disease and other organ/tissue-specific manifestations, including autoimmune disease.	13,802	15,089	All populations		

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RESEARCH

Agency: National Institutes of Health

Goal: Enhance understanding of the etiology and pathogenesis of HIV infection.

Objective 1: Support research to further understanding of HIV immunopathogenesis.

Action Steps: Delineate the cellular and molecular mechanisms associated with viral immunopathogenesis.

~~Conduct and support research on the etiology and pathogenesis of HIV infection to define the mechanism by which the virus causes disease~~

Objective: ~~Etiology and Pathogenesis~~

~~Action Steps:~~ Delineate the cellular and molecular mechanisms associated with the viral immunopathogenesis of HIV-related immune dysfunction

Descriptions: Delineate the direct and indirect mechanisms underlying HIV-induced depletion and dysfunction of target cells/tissues;

Define the virologic (load and phenotype), immunologic (specific and nonspecific), genetic, and environmental factors that contribute to disease progression and nonprogression;

Delineate the molecular mechanisms by which virus-derived factors regulate HIV replication and pathogenesis, with special emphasis on the use of primary virus isolates and cells;

Delineate the role of immune activation and host factors, including cytokines, in HIV replication and pathogenesis;

Delineate the role of lymphoid organs, including mucosal-associated lymphoid tissue, in HIV pathogenesis;

Further develop and utilize experimental models to examine the pathogenesis of lentiviral infections;

Delineate the role of lymphoid and hematopoietic precursor cells and their microenvironment in immune impairment;

Develop new assay systems for effective measurement of changes in viral load and host immune function that are predictive of disease progression;

Delineate the range of cell types infected by HIV in vivo

and their potential role as viral reservoirs; and

Establish and expand collaborative programs to facilitate sharing of key patient samples, animal model resources, and laboratory reagents.

Objective 2: Support research to enhance understanding of HIV-related immune dysfunction.

Action Steps: Delineate the molecular and cellular mechanisms of transmission and establishment of infection and their impact on disease progression.

FY 95: 201,040

FY 96: 217,368

~~**Populations Served:**~~ ~~**Populations Served:**~~ All populations

~~**Constituency Involvement:**~~

~~**Unmet Need:**~~

~~Objective: Etiology and Pathogenesis~~

~~Action Steps:~~ Delineate the molecular and cellular mechanisms of transmission and establishment of infection and their impact on disease progression

Descriptions: Define the cellular and immune mechanisms that inhibit/enhance the early events in establishing HIV infection;

Determine the impact of early events in the establishment of HIV infection on the clinical course of disease;

Determine the cell or tissue type that serves as the portal of entry of HIV and the impact of STDs and other pathogenic processes that influence HIV transmission;

Determine the effects of viral genotype and load on transmission of cell-free and cell-associated virus;

Determine the roles of specific and nonspecific mucosal immunity and host factors that inhibit/enhance HIV transmission;

Determine the mechanisms of vertical HIV transmission; and
—and

Elucidate unique aspects of HIV transmission and disease progression in underresearched populations.

Objective 3: Support research to enhance understanding of HIV-related malignancies.

Action Steps: Elucidate the etiologic factors and cofactors in the pathogenesis of HIV-related malignancies.

~~FY 95:~~ 28,140

~~FY 96:~~ 34,233

~~Populations Served:~~ All populations

~~Constituency Involvement:~~

~~Unmet Need:~~

~~Objective: Etiology and Pathogenesis~~

~~Action Steps:~~ Elucidate the etiologic factors and cofactors in the pathogenesis of HIV-related malignancies

Descriptions: Elucidate the role of HIV infection, immune dysfunction, and interactions with potential cofactors in the development of HIV-associated malignancies;

Identify the characteristics of the host that predispose to development of malignant disease, including genetic, hormonal, growth factor, cytokine, and immunologic characteristics; and

Identify the molecular correlates of HIV-associated malignancies, including but not limited to oncogenes, tumor suppressor genes, tumor promoters and carcinogens, and viral and microbial genes and proteins.

Objective 4: Support research to enhance understanding of HIV-related neuropathogenesis.

Action Steps: Elucidate the pathogenic mechanisms involved in HIV-associated neurological diseases.

~~FY 95:~~ 28,544

~~FY 96:~~ 28,941

~~Populations Served:~~ All populations

~~Constituency Involvement:~~

~~Unmet Need:~~

~~Objective: Etiology and Pathogenesis~~

~~Action Steps:~~ Elucidate the pathogenic mechanisms involved in HIV-associated neurological diseases

Descriptions: Investigate the contributions of viral infection and virally induced indirect factors (in neuronal and non-neuronal cells) to nervous system impairment;

Delineate how HIV enters and persists in the nervous system and causes functional impairment;

Investigate both biological and environmental factors that may affect nervous system function in the context of HIV disease; ~~Investigate both biological and environmental factors that may affect nervous system function in the context of HIV disease, using neurological and appropriate neuropsychologic assessment tools;~~

Study the effects of neurotrophins and immunoregulatory and proinflammatory cytokines on both host and viral gene expression;

Delineate the role of OIs and drug treatment in neurologic complications of AIDS, including peripheral neuropathies, hearing and visual loss, and behavioral changes;

Assess neural tissue and organs as virus reservoirs in HIV disease and as sources of specifically neurovirulent/neuroinvasive viral strains; and

Develop neuroimaging tools for correlative structural-functional studies of progressive HIV-associated neurological disorders.

Objective 5: Support research to enhance understanding of HIV-related opportunistic infections.

Action Steps: Elucidate the pathogenesis of HIV-related opportunistic infections.

Descriptions: Investigate the mechanisms of immune function that mediate protection against the OIs; ~~FY-95: 38,984~~

~~FY-96: 41,067~~

~~Populations Served:~~ All populations

~~Constituency Involvement:~~

~~Unmet Need:~~

~~Objective: Etiology and Pathogenesis~~

~~Action Steps: Elucidate the pathogenesis of HIV-related opportunistic infections~~

~~Descriptions: Elucidate the mechanisms of immune function that mediate protection against the OIs,~~

Develop *in vitro* techniques and animal models, where needed, to propagate the opportunistic micro-organisms and conduct studies designed to provide details of the basic biology and pathogenic mechanisms of these micro-organisms;

Identify and elucidate the genetic and environmental risk factors associated with susceptibility, development, and progression of opportunistic infections;

Develop and validate diagnostic assays for the reliable and rapid identification of HIV-associated opportunistic infections;

Study the effects of OIs on immune dysfunction; and

Elucidate immunologic markers that are correlative with disease progression for HIV-associated OIs and develop assays to accurately monitor these markers as a function of therapy.

Objective 6: Support research to enhance understanding of HIV-related wasting syndrome.

~~FY 95: 32,222~~

~~FY 96: 35,151~~

~~Populations Served: All populations~~

~~Constituency Involvement:~~

~~Unmet Need:~~

~~Objective: Etiology and Pathogenesis~~

Action Steps: Elucidate the etiology and pathophysiology of HIV-related wasting, failure to thrive, and growth retardation.

~~and growth retardation~~

Descriptions: Define alterations in body composition, nutritional status, metabolic patterns, energy balance, and growth and development associated with HIV infection; and

Elucidate the pathogenesis of HIV-associated wasting and impaired growth and development, including the roles of cytokines, malabsorption, anorexia, opportunistic infections, HIV, and other factors.

Objective 7: Support research to enhance understanding of HIV-related organ and tissue disorders.

~~FY 95: 2,931~~

~~FY 96: 2,918~~

~~Populations Served:~~ All populations

~~Constituent Involvement:~~

~~Unmet Need:~~

~~Objective: Etiology and Pathogenesis~~

Action Steps: Elucidate the etiology and pathogenesis of HIV-related organ/tissue-specific disorders, such as HIV-associated renal, gastrointestinal, endocrine, cardiopulmonary, autoimmune, and other diseases

Descriptions: Investigate the etiologic and pathogenic mechanisms of HIV-associated enteropathy, including the role of HIV, opportunistic infections, tumors, and other factors;

Identify host, viral, environmental, and other factors responsible for the pathogenesis and progression of HIV-associated nephropathy;

Elucidate the etiology and pathogenesis of endocrine dysfunction and the role of alteration in the endocrine/immune axis in progression of HIV disease; and

Elucidate the etiology and pathogenesis of HIV-related cardiopulmonary disease and other organ/tissue-specific manifestations, including autoimmune disease.

FY 95: 345,663

FY 96: 374,767

~~Pop. Served:~~ All populations

~~Constituency Involvement:~~ Researchers, clinicians, community and patient representatives, NIAID Advisory Council, ARAC, and OAR Advisory Committees. Others?

~~Unmet Needs:~~ The NIH FY 1996 Plan and Budget Estimate for Scientific Opportunities in HIV-Related Research identified areas for further productive research in this area in the amount of \$46,216 over the FY 96 figure. 13,302

~~FY 96:~~ 15,089

~~Populations Served:~~ All populations

~~Constituency Involvement:~~

~~Unmet Need:~~

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FY 96 Bypass

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

(Dollars in thousands)

Etiology and Pathogenesis

	FY 1994 Estimate	FY 1995 Estimate	FY 1996 By-pass
Objective 1 Delineate the cellular and molecular mechanisms associated with the viral immunopathogenesis of HIV-related immune dysfunction.	\$111,237	\$122,052	\$168,661
Objective 2 Delineate the molecular and cellular mechanisms of transmission and establishment of infection and their impact on disease progression.	80,967	86,862	114,152
Objective 3a Elucidate the etiologic factors and cofactors in the pathogenesis of HIV-related malignancies.	9,576	8,271	16,795
Objective 3b Elucidate the pathogenic mechanisms involved in HIV-associated neurological diseases.	39,223	41,131	47,363
Objective 3c Elucidate the pathogenesis of HIV-related opportunistic infections.	34,919	35,651	48,775
Objective 3d Elucidate the etiology and pathophysiology of HIV-related wasting, failure to thrive, and growth retardation.	4,855	5,163	6,638
Objective 3e Elucidate the etiology and pathogenesis of HIV-related organ/tissue-specific disorders, such as HIV-associated renal, gastrointestinal, endocrine, cardiopulmonary, autoimmune, and other diseases.	12,814	15,250	18,599
TOTAL, Etiology and Pathogenesis	293,591	314,380	420,983

FY 96 plan

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

(Dollars in thousands)

Etiology and Pathogenesis

	FY 1994 Actual	FY 1995 Appropriation	FY 1996 Pres. Bud.
Objective 1 Delineate the cellular and molecular mechanisms associated with the viral immunopathogenesis of HIV-related immune dysfunction.	\$196,987	\$201,040	\$217,368
Objective 2 Delineate the molecular and cellular mechanisms of transmission and establishment of infection and their impact on disease progression.	24,961	28,140	34,233
Objective 3a Elucidate the etiologic factors and cofactors in the pathogenesis of HIV-related malignancies.	27,278	28,544	28,941
Objective 3b Elucidate the pathogenic mechanisms involved in HIV-associated neurological diseases.	38,769	38,984	41,067
Objective 3c Elucidate the pathogenesis of HIV-related opportunistic infections.	32,445	32,222	35,151
Objective 3d Elucidate the etiology and pathophysiology of HIV-related wasting, failure to thrive, and growth retardation.	2,802	2,931	2,918
Objective 3e Elucidate the etiology and pathogenesis of HIV-related organ/tissue-specific disorders, such as HIV-associated renal, gastrointestinal, endocrine, cardiopulmonary, autoimmune, and other diseases.	10,322	13,802	15,089
TOTAL, Etiology and Pathogenesis	333,564	345,663	374,767

Therapeutics