F. AIDS/HIV-RELATED RESEARCH

INTRODUCTION
The human immunodeficiency virus (HIV) is a pathogenic retrovirus that causes acquired immunodeficiency syndrome (AIDS) and its related diseases in humans. Because of its high rate of mortality, AIDS has become the center of worldwide attention; research into the development of safe and effective therapies, as well as methods of prevention of this fatal disease, is currently a national public health priority.

HIV-related research centers on both biomedical and behavioral questions. Biomedical research has been characterized as falling into five major scientific categories: "(1) the study of the distribution of HIV infection and AIDS in the population (epidemiology) and the pattern of disease progression (natural history); (2) the identification and characterization of the virus that causes AIDS (etiologic agent); (3) delineation of the mechanisms by which the virus destroys the immune system and produces disease (pathogenesis); (4) the development and testing of potential therapies for HIV infection and its complications; and (5) the development and evaluation of potential AIDS vaccines" [Hamburg and Fauci (1989), p. 22].

Behavioral research on HIV focuses on: (1) identifying the social, psychological, and behavioral conditions of disease transmission and prevention; (2) the effects of psychological state on immunosuppression; and (3) the role of psychology in alleviating the distress experienced by persons affected by HIV infection (including families, friends, and persons at risk).

IRB CONSIDERATIONS
Research designed to answer the many biomedical and behavioral questions presented by HIV poses numerous ethical concerns. Primary among them are considerations of privacy, confidentiality, and justice (fairness in the distribution of the benefits and risks of research). The subjects involved in HIV-related research, HIV-infected individuals, and persons at risk of HIV infection, are particularly vulnerable, both because of their disease status, and because the disease disproportionately affects certain populations: male homosexuals and bisexuals, intravenous drug users, minorities, and, increasingly, women and children. [See Guidebook Chapter 6, "Special Classes of Subjects."]

An overriding concern in HIV research is confidentiality. Subjects included in HIV-related studies are understandably concerned about the confidentiality of the data, since breaches in confidentiality could have severe adverse consequences such as loss of employment or insurance coverage, or criminal charges. OPRR guidance on HIV studies states that:

where identifiers are not required by the design of the study, they are not to be recorded. If identifiers are recorded, they should be separated, if possible, from data and stored securely, with linkage restored only when necessary to conduct the research. No lists should be retained identifying those who elected not to participate. Participants must be given a fair, clear explanation of how information about them will be handled.

As a general principle, information is not to be disclosed without the subject's consent. The protocol must clearly state who is entitled to see records with identifiers, both within and outside the project. This statement must take account of the possibility of review of records by the funding agency.... [OPRR Reports, Dear Colleague Letter (December 26, 1984), p.3.]

IRBs should also consider whether and how information from HIV-related studies will be recorded in subjects' medical records, and may decide to impose limits on the recording of such data. Before agreeing to participate in an
HIV study, subjects should be informed of exactly what information will be recorded, and whether any state laws require the reporting of HIV infection or other disclosures of information. The research protocol should also deal with the possibility of attempts under compulsory legal process to force disclosure of records, how such attempts will be responded to, and whether individuals will be notified of such attempts. [See also the Guidebook Chapter 3, Section D, "Privacy and Confidentiality," which deals with certificates of confidentiality and subpoenas.] The protocol should specifically set forth how to respond to requests by third parties who have authorizations for disclosure of information signed by subjects. An extensive set of guidelines for confidentiality in research on HIV has been developed by a group of prominent scholars, practitioners, and community members, and may be helpful to IRBs considering HIV-related protocols. [See Bayer, Levine, and Murray (1984).]

The PHS has an established policy on the issuance of certificates of confidentiality to projects that are subject to the reporting of communicable diseases to state and local health departments. The policy applies to projects that intend routinely to determine whether its subjects have communicable diseases, and that are required to report them under state law. Certificates will be issued: (1) where the referring treating physicians assure the project that they have complied with reporting requirements; (2) the investigator has reached an agreement with the health department about how he or she will cooperate with the department to help serve the purposes of the reporting requirements (unless the investigator can show why such cooperation is precluded); and (3) only where disclosures of identifiable information about subjects comply with regulations on subject protection, and are explained clearly to subjects prior to their participation [Mason (August 9, 1991)]. [See also Guidebook Chapter 3, Section D, "Privacy and Confidentiality."]

The giving of voluntary consent, axiomatic to all research involving human subjects, applies equally in HIV-related research. Complicating the consent issue, however, is that HIV-related illness, particularly in its later stages, can cause dementia, thus affecting the ability of subjects to give consent or continue to consent to ongoing research. Research protocols should deal with this possibility; IRBs should ensure that subjects in this particularly vulnerable condition are adequately protected. [See also Guidebook Chapter 6, Section D, "Cognitively Impaired."]

Research on vaccines and treatments poses some of the most difficult questions, including the level of acceptable risk to subjects when the disease is fatal and no effective therapy is available; whether HIV-infected patients can be used as a placebo group that is not given experimental treatments; how subjects should be selected to receive experimental therapies; whether and under what circumstances healthy and at-risk but not-yet-HIV-infected persons can ethically be asked to participate in vaccine trials.

Clinical Trials of HIV-Related Therapies. Randomized clinical trials (RCTs) and the ethical problems surrounding their use is discussed in Guidebook Chapter 4, Section H and related Guidebook Sections. This Section will focus on questions of particular concern for research involving HIV-infected individuals.

Randomized, controlled clinical trials are considered the research design most likely to yield valid scientific results for the evaluation of the safety and effectiveness of experimental therapies. Ethical use of RCTs depends on the existence of both the ability to state a null hypothesis (also called "theoretical equipoise") and that there be no other therapy known to be more effective than the one being studied in the RCT. A report produced by a working group on clinical HIV research convened by the American Foundation for AIDS Research argues, however, that when no known effective alternative therapy exists, as is presently the case with HIV, it may be justified to consider the use of other forms of controls such as historical controls (that is, to compare the effects of the therapy in the trial population with the treatment experiences of patients with the same disease before use of the experimental therapy) [Levine, Dubler, and Levine (1991), pp. 3, 6]. The justification for this position is that the conditions of "clinical equipoise" (a situation in which there is a "current or likely dispute among expert members of the clinical community as to which of two or more therapies is superior in all relevant respects," and which is also necessary for an RCT to be ethical) are not satisfied [id.]. The working group issued a document that included 57 recommendations on the conduct of clinical research on HIV, which IRBs may wish to consult [id.].

The use of placebo controls is particularly problematic. As a general matter, where the disease is lethal or seriously debilitating, as in the case of HIV, the use of placebo controls in place of an active control is difficult to justify ethically, despite the possibility that the experimental therapy is harmful (e.g., toxic) rather than therapeutic. In the language of the Belmont Report, the question of the use of control groups in this situation is one of beneficence:
Are potential benefits maximized in all arms of the trial? The fatal nature of the disease leaves patients in a
desperate position in which many seek any promising treatment. It has been suggested that the question may be
resolved in favor of placebo controls only under two conditions: (1) when there is either no known effective therapy
that can be used as an active control, or subjects are persons who cannot tolerate a known effective therapy; and (2)
the trial therapy is "so scarce that only a limited number of patients can receive it" [Levine, Dubler, and Levine
(1991), p. 8]. A fair way to then assign subjects to the active and control arm(s) is through a lottery [id.] [See also
Macklin and Friedland (1986), pp. 277-79, and Guidebook Chapter 4, Section H, "Clinical Trials," and related
Guidebook Sections.]

Once there is sufficient evidence of either a beneficial therapeutic effect, unacceptable side effects, or indication that
there is a very low probability of establishing statistically significant research results, the trial should be stopped or
the protocol should be modified [Macklin and Friedland (1986), pp. 177-78]. Where an experimental therapy is
shown to have a beneficial therapeutic effect, the control group should be offered access to the experimental therapy.
Prospective subjects should be informed of the probability of being assigned to the control group, the risks
associated with being assigned to either the treatment or control group, the criteria that will be used for determining
a beneficial effect sufficient to discontinue the control arm of the trial, and the consequences of discontinuing the
control arm (e.g., will control subjects be added to the experimental group, will they be given the experimental
therapy on a treatment basis, will they be offered the experimental therapy only if they pay for its cost, or will they
be dropped from the study without access to the experimental therapy). It should be made clear to prospective
subjects that the likelihood of the experimental therapy having harmful effects may well be as great as the likelihood
of its having beneficial effects.

The selection and recruitment of subjects is also of concern. Subjects for clinical trials are often recruited on the
recommendation of treating physicians. Unable or unwilling to obtain medical care, many individuals have been
excluded from participation in trials. Others, not aware of the existence of trials, are also left out. Care should be
taken to ensure the appropriate inclusion of women, children and adolescents, and minority groups in HIV-related
clinical trials. Note also that IRBs must follow the additional protections provided in the DHHS regulations
wherever applicable. [See Subpart B (fetuses, pregnant women, and human in vitro fertilization), Subpart C
(prisoners), and Subpart D (children).]

When reviewing protocols involving HIV-infected or at-risk individuals or persons, IRBs should consider including
(as consultants, if they are not already members) persons knowledgeable about and experienced in working with
such subjects [Federal Policy § ____107]. Some investigatory groups have used "community advisory committees" as
a means both of better understanding the concerns of the subject population and of educating the HIV-infected
community about clinical research.

Vaccines. The testing of AIDS/HIV vaccines in human subjects raises substantial ethical issues. First and foremost
is the question of risks and benefits. Limited availability of animal data means that many of the risks that might be
associated with an AIDS/HIV vaccine (e.g., vaccine-induced immunotoxicity) are unknown. Nonetheless, the
importance of developing an AIDS/HIV vaccine is felt to outweigh these uncertainties. From the standpoint of
protecting the welfare of human subjects, however, the lack of knowledge about risk and the potential for the
existence of serious risk must be clearly communicated and consented to by prospective subjects.

While all viral vaccines pose risks, HIV vaccines may, in addition, increase the risk of acquiring the disease when
subsequently exposed to HIV. Also, because of potential immune tolerance, subjects may not be able to be
vaccinated with a different AIDS/HIV vaccine if the experimental one proves ineffective. Persons with whom the
subject is in close contact may also be at risk of transmission of recombinant viruses (through the injection site).
IRBs should consider the degree to which investigators have minimized these risks, and ensure that subjects are
adequately informed of and consent to these and other potential physical risks.

Another issue about which subjects must be informed is the effect of participation in the trial on their HIV serostatus
and the potential social ramifications of changes in HIV serostatus. Just as persons infected with HIV through more
usual means of transmission (e.g., sexual activity, the use of intravenous drugs, or blood transfusions) will test
positive on antibody screening tests, so too will persons immunized with experimental AIDS/HIV vaccines. There
may be limited access to diagnostic methods for distinguishing between persons who are HIV-infected and persons
who have received HIV vaccinations. One way to help alleviate this problem is for trial sponsors to follow the lead of the National Institute of Allergy and Infectious Diseases (NIAID), and provide subjects with documentation certifying participation in the vaccine trial. Nonetheless, participation in AIDS/HIV vaccine trials in itself may carry a social stigma.

### Informing Subjects of Their HIV Serostatus

Some research protocols involve screening blood samples for HIV seroprevalence or other procedures through which subjects' HIV serostatus will be discovered. In addition to ensuring that the confidentiality of this information and all research data is scrupulously provided for, and that subjects will be informed that they will be tested and of the risks and benefits involved, IRBs will need to consider the circumstances under which subjects should or must be told of their HIV serostatus. PHS policy requires that where HIV testing is conducted or supported by the PHS, individuals whose test results are associated with personal identifiers must be informed of their own test results and provided the opportunity to receive appropriate counseling unless the situation calls for an exception under the special circumstances set forth in the policy. Under the PHS policy, individuals may not be given the option "not to know" their test results, either at the time of consenting to be tested or thereafter. The acceptable "special circumstances" include such compelling and immediate reasons as an indication that a given individual would attempt suicide if informed that he or she was HIV seropositive; that extremely valuable knowledge might be gained from research involving subjects who would be expected to refuse to learn their HIV antibody results; or research activities conducted at foreign sites where cultural norms, the health resource capabilities, and official health policies of the host country preclude informing subjects of their HIV serostatus. Subjects should also be informed early in the consent process of any plans to notify subjects' sexual or needle-sharing partners. [See OPRR Reports ("Dear Colleague" letters dated December 26, 1984 and June 10, 1988).] Several commentators have taken issue with the position that subjects should be told of their serostatus regardless of their wishes. [See, e.g., Novick (1986) and Dubler (1986); compare Landesman (1986).] While this issue may be controversial, opportunities for early intervention weigh in favor of policies that require informing subjects of their HIV serostatus.

### Counseling

Whenever subjects will be informed of their HIV serostatus, appropriate pretest and post test counseling must be provided. Counselors should be qualified to provide HIV test counseling and partner notification services. IRBs should ensure that such provisions are made. [See OPRR Reports ("Dear Colleague" letters dated December 26, 1984 and June 10, 1988)]

See also Guidebook Chapter 2, Section B, "Food and Drug Administration Regulations and Policies" (discussing expanded availability of investigational agents), and Chapter 4, "Considerations of Research Design."

### Behavioral Research

Research on behavioral questions related to HIV often centers on what behavioral factors contribute to disease transmission and dissemination, as well as other psychosocial factors related to HIV (e.g., the relationship of stress to immunosuppression). The American Psychological Association has expressed concerns for subjects' privacy, protections against the intrusive nature of behavioral research (because research on risk factors and modes of disease transmission often probes intimate details of subjects' lives such as sexual practices and past history of illicit drug use), confidentiality, and the need to carefully debrief subjects.

### Vulnerability of Subjects

In addition to the ethical issues raised by the conduct of HIV-related research itself, the involvement of HIV-infected subjects presents special concerns to which IRBs should be sensitive. As noted above, homosexual and bisexual men, intravenous drug users, minorities, and, increasingly, women and children constitute the bulk of the HIV-infected population. Their vulnerability as subjects arises primarily because their HIV status presents special concerns of confidentiality and privacy. Knowledge of a person's HIV status can lead to discriminatory practices on the part of employers, landlords, insurance companies, and others. That HIV disproportionately affects certain populations heightens the threat of inappropriate disclosure of HIV-related data. In addition, characteristics of the progression of AIDS, which can include both physical incapacity and loss of mental capacity, can impinge on subjects' ability to exercise their right to autonomy in the course of the research. IRBs can ensure that AIDS patients and other HIV-infected subjects are adequately protected by viewing each subject first and foremost as an individual. Researchers working with HIV-infected persons must be capable of dealing with social, emotional, and psychological, as well as physical factors. Taking such a multifaceted approach to working with this subject population is a means of incorporating the various necessary cultural and filial influences into the
research relationship. Researchers should seek the advice and consultation of experts in these and other relevant fields as necessary.

Another factor that heightens the vulnerability of HIV-infected individuals is the lack of available treatment alternatives. At present, HIV infection is believed uniformly to progress to AIDS; no available treatment cures AIDS, although some therapies postpone the onset and severity of opportunistic infection. Prospective subjects in HIV-related studies may, therefore, agree to participate in research out of a hope for a cure, which may or may not be realistic. But while IRBs should protect subjects against exposure to excessive risk, they must also guard against paternalism. Despite the fatal nature of the disease, there may be risks to which individuals should not be asked to subject themselves; despite their vulnerability, however, prospective subjects should be given the opportunity to participate and obtain whatever benefits may be available. IRBs should consider protocols and make their evaluation of the requisite factors (i.e., the level of risk involved, a positive risk/benefit ratio, equitable selection of subjects, informed consent, and protection of privacy and confidentiality) with this concern in mind. The additional protection that IRBs can provide is to ensure that the protocol, its goals, and the research benefits and risks are clearly and simply delineated and communicated to the subject. It is important that participation in the research not engender either false hopes or a sense of hopelessness. Furthermore, IRBs should try to ensure that access to health care does not serve as a lure for participation.

IRBs need to review participant eligibility requirements closely and extensively monitor the data collection and analysis process. The consent process should also be carefully considered, with special attention to provisions for determining mental capacity to consent and alternative means for obtaining consent, where necessary. [See Guidebook Chapter 6, Section D, "Cognitively Impaired."] The duration of any health care to be rendered through participation, including counseling, should be thoroughly reviewed with subjects. As noted above, subjects must be clearly and explicitly informed of any applicable law or policy that requires either partner notification or notification to health authorities of subjects' HIV serostatus or disease status.

Finally, many HIV-infected persons are economically and/or educationally disadvantaged, and may need adjunct services or other help to be able to participate in research. To ensure that all affected groups have an adequate opportunity to participate, IRBs should give some thought to how investigators might meet these needs, thereby encouraging a broader distribution of the risks and benefits of HIV-related research.

Availability of Drugs and Other Therapeutic Agents for AIDS and HIV-Related Conditions. The availability of experimental drugs and other therapeutic agents for the treatment of AIDS and other HIV-related conditions has been highly controversial. Two mechanisms, Treatment INDs, and a subset of Treatment INDs, Parallel Track programs, have been developed by the FDA to meet this concern. They are discussed in the Guidebook in Chapter 2, Section B, "Food and Drug Administration Regulations and Policies."

POINTS TO CONSIDER

1. Pre-screening clinical study participants for HIV antibody status: See the list of questions provided in OPRR Reports, "Points to Consider for Institutional Review Boards (IRBs) Regarding the Screening of Volunteers for HIV Antibody Status," (circa August, 1989).

2. Is the composition of the IRB membership appropriate for an adequate review of the protocol? Should the IRB seek consultation with laypersons, persons with AIDS or who are HIV-infected, or members of the HIV-affected community?

3. Are subjects' privacy and confidentiality adequately protected? Are certificates of confidentiality appropriate?

4. Does the consent process provide adequately for the special needs of subjects participating in HIV-related research, including subjects with impaired mental capacities and the difficulties of communicating the risks presented by drug and vaccine trials?
5. Will the informed consent process clearly inform the subject of all pertinent information (e.g., the circumstances under which the investigator may terminate the subject's participation without the subject's consent; the circumstances under which the subject may withdraw from participation and the costs associated with withdrawal; the financial costs of participation; how medical care will be handled in the event of injury or onset of opportunistic illness; whether partner notification and/or disease status reporting to health authorities will occur)?

6. Is there a mechanism for dealing with changes in mental capacity and continuing consent? Who will give consent in the event of diminished mental capacity or lack of majority (in the case of children)? Is it necessary to obtain subjects' assent?

7. Are protections against coercion in place?

8. If the protocol involves a clinical trial, have appropriate FDA clearances and an approved IND been obtained?

9. Does the protocol provide for adequate monitoring of all subjects for adverse reactions? Are provisions made for early termination?

10. Will subjects be informed about what to do and whom to contact in case of a serious adverse reaction or research-related injury?

11. Will subjects involved in behavioral research be adequately debriefed? Are intrusions into subjects' privacy minimized?

**APPLICABLE LAWS AND REGULATIONS**

Federal Policy for the protection of human subjects

21 CFR 50 [FDA: Informed consent]
21 CFR 56 [FDA: IRB review and approval]
21 CFR 312 [FDA: New drugs for investigational use]
45 CFR 46, Subparts B-D [DHHS: Protection of human subjects]

*Federal Register* 57 (April 15, 1992): 13250-13259 [FDA: Parallel track policy]

State and local laws concerning the reporting of HIV-related information

Public Health Service policies related to AIDS research:


James O. Mason [Assistant Secretary for Health]. "Certificates of Confidentiality — Disease Reporting" [Memorandum]. (August 9, 1991.)

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