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The term acquired immunodeficiency syndrome (AIDS) is a definition developed by the Centers for Disease Control to explain the epidemic of immunosuppression first seen in the United States among gay and bisexual men and intravenous drug users in the early 1980s. It is now known that the human immunodeficiency virus (HIV) is the necessary agent for the compromise of the immune system which results in AIDS; however, there is a wide range of manifestations associated with HIV infection. Individuals with AIDS tend to have severe opportunistic infections or malignancies, and the vast majority of individuals die within two years after the diagnosis. At least a fourth of the individuals with HIV infection in one study were found to remain asymptomatic after seven years of infection. Between the long period of asymptomatic infection and the development of life-threatening opportunistic infections, individuals may develop subacute manifestations of HIV infection. Some individuals may develop constitutional symptoms, without any other medical explanation. The clinical use of tests of immunologic function as well as newer tests that may describe the type of HIV infection, such as the serum antigen test, may enhance the ability of clinicians to give infected patients more specific information as to their prognosis. As newer therapies are developed, the utilization of newer diagnostic tests may allow for staging more rational treatment plans. The data suggesting increasing efficacy of Azidothymidine (AZT), as well as the development of newer chemotherapeutic agents, may lead to more widespread HIV testing in order to detect infection at early stages and intervene with specific therapies. Use of the test as a means of altering behavior remains controversial. The development of newer therapies is hindered by the need to avoid exposing HIV-infected individuals to agents that subsequently turn out to be harmful, such as HPA-23 and Suramin. But this must be balanced with the urgent need of individuals to try promising therapeutic agents. Preliminary data suggest that individuals who are treated with AZT at earlier stages of HIV infection may do better; thus, there may be a move in the future to treat people with AZT. The clinical dilemma will persist for some time to come, and the cost of care for individuals with AIDS and HIV infection will be extremely high. Although the illness is frequently fatal, it is most appropriate to be considerate of

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the individual's desire to have more aggressive therapies, given the variability of HIV infection for each person and the fact that new therapeutic breakthroughs are being made every day.

The AIDS epidemic is profoundly affecting the general public regarding issues of social policy, ranging from the sexual counter-revolution to how one deals with primeval fears of contagion in the age of instant global transport. Medical clinicians comprise one of the groups that have had to respond most to the multiple conundra associated with this epidemic. They were also among those individuals who initially recognized that something new was occurring with the disease in the early 1980s. Nosology is that branch of medical science which deals with the classification of diseases, and at the outset of what is now perceived as a global problem, the new epidemic was a clinically complicated nosological question. Young males, predominantly gay men with multiple sexual partners, as well as a few intravenous drug users, in a discrete number of cities — that is, New York City, San Francisco, and Los Angeles — were perceived to be developing illnesses associated with deranged immunoregulation. The first published report in the medical literature regarding what is now known as the AIDS epidemic was in the *Morbidity and Mortality Weekly Report*, a newsletter of the Centers for Disease Control (CDC), which described several cases of *Pneumocystis carinii* pneumonia in Los Angeles.[1] The authors noted that all of the infected individuals were exposed to cytomegalovirus and wondered whether this virus could be playing a role that could explain why homosexually active males were developing a disease previously associated with individuals who were iatrogenically immunocompromised or malnourished. The subsequent reports of Kaposi's sarcoma,[2] which may occur in immunocompromised individuals, and the appearance of *Pneumocystis carinii* in individuals who presumably could have been infected via contaminated needles, helped to buttress the possibility that a specific infectious agent that could be transmitted sexually and via blood was resulting in the epidemic of immunosuppression. However, for several years an ongoing debate raged, with at least three sides. Some felt that this epidemic was due to a new infectious agent; some thought it was due to agents already present which might have undergone evolution (such as cytomegalovirus, or a combination of infectious agents); and others felt that the epidemic represented a burnout of the immune system, because high-risk individuals tended to be exposed to multiple agents, drugs, and other nonspecific antigens that tended to overwhelm their host defenses. Subsequent elucidation of the retroviral etiology of HIV infection,[3, 4] which was abetted by careful epidemiological studies linking new risk groups and helping to develop a very tight case that HIV was the etiologic agent,[5] has not necessarily diminished the diagnostic and therapeutic questions facing clinicians today. More than six years into the epidemic, clinicians still cannot accurately tell individuals who are infected with HIV when and whether they will develop AIDS and whether they should take Azidothymidine (AZT) or one of the other, less studied treatment regimens.

Definition of the Clinical Spectrum of the Epidemic

When the epidemic of immunodeficiency was first recognized in the early 1980s, the Centers for Disease Control was given the responsibility of trying to define a process whose origin was unclear, whose etiology was unknown, and whose natural history was

uncharted. Fortunately, the revolution in immunologic understanding and diagnostic techniques which had occurred in the late 1970s allowed for the conceptualization that a major cell that regulated many aspects of host immune response, the T-helper lymphocyte, was numerically depleted and functionally impaired. All the individuals with this type of impairment manifested one or another of an increasing number of atypical infections and neoplasms.[6] The aggregation of a specific type of immunologic impairment, specific distinctive and atypical types of illnesses, in individuals with specific risk behaviors, allowed the Centers for Disease Control to evolve a case definition of what came to be known as the acquired immunodeficiency syndrome. The dilemma that these investigators faced was how to define this process that was still so unclear without lumping into it individuals whose infections or neoplasms, or both, were due to other causes while at the same time not leaving out the increasing numbers of individuals with some evidence of T-helper lymphocyte immunologic impairment. At an early point in time, the CDC decided to take a narrow-based approach in which cases reported which related to the epidemic would be those of the sickest individuals who did not have other reasons for immunosuppression but who had one of a specific laundry list of clinical syndromes that were distinctively atypical in individuals whose immune systems were intact.[7] This approach was extremely effective in picking up individuals who had the classic signs of immunologic impairment and conditions which were the most commonly seen in the course of the epidemic, such as *Pneumocystis carinii* pneumonia and Kaposi's sarcoma. Neither of these conditions occurred with any significant frequency in individuals who were not immunosuppressed or elderly, or both.

However, other individuals developed illnesses that were not specific to immunocompromised individuals, but the severity of their manifestations suggested that they were immunologically impaired. For example, herpes simplex infection around the mouth or

Table 1

Summary of Centers for Disease Control (CDC) Classification System for HIV Infections

Group I.	Acute infection
Group II.	Asymptomatic infection*
Group III.	Persistent generalized lymphadenopathy
Group IV.	Other disease
Subgroup A.	Constitutional disease
Subgroup B.	Neurological disease
Subgroup C.	Secondary infectious diseases
Category C-1.	Specified secondary infectious diseases listed in the CDC surveillance definition for AIDS‡
Category C-2.	Other specified secondary infectious diseases
Subgroup D.	Secondary cancers‡
Subgroup E.	Other conditions

*Patients in groups II and III may be subclassified on the basis of a laboratory evaluation.

‡Includes those patients whose clinical presentation fulfills the definition of AIDS used by the CDC for national reporting.

the perirectal area is not an uncommon infection of homosexually active males who have multiple partners, but the persistence of perianal ulcerations around the rectum in the setting of immunologic abnormalities seen in blood tests was highly suggestive of the wider spectrum of the epidemic. Even more difficult for the clinician were individuals who had persistent wasting syndromes accompanied by significant weight losses, persistent fevers, and malaise, who despite extensive medical evaluations did not have specific infectious agents always identified as the source of their problems. Other individuals who are at high risk to develop AIDS continue to be well for long periods of time with asymptomatic immunologic abnormalities, or may show evidence only of persistent generalized lymph gland swelling associated with blood test abnormalities.[8, 9] Astute clinicians in the cities where the epidemic was first appreciated noted that individuals often progressed from asymptomatic conditions to those of lesser severity to the more severe opportunistic infections. Others noted that certain processes were more common in individuals with specific risk characteristics; for example, homosexually active males were more likely to have Kaposi's sarcoma than individuals who were intravenous drug users.[10]

Even before HIV was delineated as the etiologic agent, clinicians and epidemiologists expanded their vision of the epidemic to incorporate the concept of the iceberg, with those conditions defined as AIDS representing the tip of the iceberg. Progression from asymptomatic high-risk status to full-blown opportunistic infections helped to develop this concept. Even more convincing was the delineation of the similar spectrum of degrees of immunocompromise among individuals who had received blood transfusions from individuals who had subsequently developed AIDS, and among individuals from other nations who did not have any history of homosexual activity or intravenous drug use. The development of an intellectual model of a process that resulted in immunocompromise, with opportunistic infections and neoplasms subsequently supervening, was validated once HIV was isolated, and appropriate seroepidemiologic studies were undertaken which confirmed the increased prevalence of this virus in individuals with AIDS and related symptom complexes.

One might ask, Why should the arbitrary definition of AIDS continue to be reported when one can actually monitor the prevalence of the causative agent itself? Although infection with HIV is necessary for an individual to develop AIDS, it is still not clear whether all individuals who are HIV-infected will ultimately develop the full-blown syndrome. The best data that bear on this issue are derived from a hepatitis B vaccine study that took place in San Francisco from 1978 to 1980 at a clinic for sexually transmitted diseases which is run by the city health department. Of the gay and bisexual men who were found to be infected with HIV between 1978 and 1980, more than one-third developed CDC-defined AIDS by 1987, and approximately 25 percent remain completely asymptomatic.[11] The range for individuals in the middle zone includes asymptomatic immunologic abnormalities; persistent generalized lymphadenopathy; minor opportunistic infections such as thrush and zoster; and the presence of persistent constitutional symptoms. We must be careful about generalizing from this cohort, since prior to recognition of the AIDS epidemic in the early 1980s, there was no widespread education as to what constituted safer sexual practices. If repeated exposures to HIV or other sexually transmitted viruses such as cytomegalovirus and Epstein-Barr virus result in synergistic immunosuppression with the initial HIV infection, then the rates of progression from asymptomatic HIV infection from the men in this cohort could represent a worst-case scenario. However, no single study of homosexual or heterosexual exposure has indicated that unsafe sex after initial HIV infection results in more rapid immunocompromise, and

thus the data generated from this cohort can be utilized as a point of reference despite such sexual practices.

The finding that a substantial number of individuals who are HIV-infected develop full-blown AIDS does not mean that a separation in reporting of AIDS is not useful at the present time. Individuals who do not have AIDS may need to utilize many health care services, including multiple laboratory tests, medical evaluations of recurrent minor opportunistic infections, and counseling and support services. Individuals with AIDS tend to have much more severe medical illnesses; thus, monitoring the increasing number of individuals who frequently require intensive, tertiary services is a useful way to monitor health care utilization and to assist planners in projecting what types of resources it will be necessary to deploy as the epidemic continues to progress. AZT is the first drug that has been shown to assist in extending life in individuals with AIDS or with the ill-defined AIDS-related complex (ARC), a term that usually relates to constitutional symptoms associated with HIV infection. It is not known at the present time whether AZT will ultimately forestall the progression to AIDS of many individuals whose HIV infection is rapidly progressing. ("Ill-defined" is used here as a descriptor because specialists do not agree on the definition of AIDS, and therefore various articles and other writings refer to different levels of morbidity.) If current projections by the Centers for Disease Control are correct, between 1 million and 1.5 million Americans are currently infected with HIV, and by 1991 more than a quarter million of them will have developed CDC-defined infections or neoplasms that are now described as one of the conditions defined as AIDS.[12]

The Wide Spectrum of HIV Infection

Intimate sexual contact with an HIV-infected partner or the sharing of contaminated needles does not invariably result in HIV infection. In a prospective study of homosexually active male partners conducted in Boston, more than one-third of the partners were discordant (that is, one partner was seronegative and the other, seropositive) despite possible high-risk anal exposures to infected ejaculate on the part of the susceptible seronegative partner.[13] Whether certain individuals are intrinsically more able to resist infection with HIV or whether some infected individuals are less capable of transmission is not clear at the present time. Some lines of data suggest that individuals may become more efficient in the transmission of HIV infection the longer they carry the virus. This observation has been made concerning hemophiliacs and their spouses;[14] concerning homosexually active male partners; in the recipients of infected blood;[15] and in perinatal studies.[16]

Once an individual has become infected with HIV, it most often takes between three and twelve weeks to develop detectable antibodies. The vast majority of individuals have detectable markers for HIV infection by six months, although there are rare individuals who have not developed HIV antibodies after several years of follow-up. Newer diagnostic tests, such as the detection of serum antigen, may permit demonstration that an HIV exposure has occurred prior to the development of antibody. At the time of seroconversion, individuals may manifest a number of symptoms, including a mononucleosis-type syndrome; rashes that may be hivelike or maculopapular; an aseptic meningitis; and unexplained fevers.[17, 18] However, many individuals, perhaps most, may remain completely asymptomatic for several years after becoming HIV-infected. In response to the increasing understanding of the wide spectrum of HIV infection, the CDC has developed a classification system (see table 1) which describes individuals with acute infection, asymptomatic infection, and persistent generalized lymphadenopathy, as well as those

who have clinically significant HIV infection, that is, opportunistic neoplasms and infections, neurological syndromes, or constitutional symptoms, or a combination of these.[19] The individuals in the first three groups of the CDC classification system have highly variable courses. For example, some persons may have persistent HIV-related lymphadenopathy for many years without any other subsequent untoward sequelae.[20] However, once individuals develop systemic complaints and constitutional symptoms, there may be a rapid progression to more severe complications of HIV infection which are subsumed under the acronym AIDS (see tables 2 and 3).

Individuals who have early HIV infection present difficult decisions for clinicians regarding questions of appropriate interventions to prevent them from further immunocompromise. Several studies are now under way in the AIDS Treatment Evaluation Units (ATEUs) that are funded by the National Institutes of Health (NIH). These studies will attempt to determine whether asymptomatic seropositive individuals will benefit from receiving AZT. However, it may take several years to answer this question. In the meantime, many worried individuals who are aware that a subsequent clinical decline is a frequent outcome of long-standing asymptomatic infection try to obtain drugs through black markets — drugs that may be homemade, such as AL-721, or that may be smuggled in from Mexico, such as Ribavirin. Another dilemma for clinicians concerns the decision about how aggressively to diagnostically evaluate individuals with generalized lymphadenopathy. At the early phase of the epidemic, many clinicians were more likely to do lymph node biopsies on patients who had persistent swollen glands, even in the absence of constitutional signs. It has subsequently emerged that without the evidence of hematologic or clinical abnormalities, biopsy most often results in finding a lymph node whose histologic pattern is termed "reactive follicular hyperplasia," a pattern that tells the health care workers only that the lymph gland is "turned on," without conveying any specific prognostic information.[21]

Whether or not an individual has swollen lymph glands, the onset of so-called constitutional symptoms — that is, persistent fevers, chills, sweats, weight loss, and malaise — is generally a negative prognostic sign.[22] Obviously, individuals with HIV infection may have any of these symptoms for other reasons, some of which may or may not portend the onset of an opportunistic infection. Very often, HIV-positive individuals and their clinicians are in a state of worried anticipation once these types of symptoms supervene. An episode of influenza can be emotionally upsetting and result in unnecessary diagnostic studies in anxious seropositive persons. The chronicity of symptoms, generally lasting more than a month, may be a sign that the HIV infection has resulted in a new state of more severe immunocompromise and susceptiblity to opportunistic infection. Individuals with constitutional symptoms generally need to have an extensive medical workup, since some of the conditions they have may be treatable and may be more amenable to therapy if diagnosed early. However, HIV infection itself can result in any of these symptoms, as well as a wide range of neurological findings, though some individuals may undergo expensive workups without obtaining a definitive answer. However, one cannot take the attitude that if the workup initially is negative, there is no use in repeating it if further symptoms develop. Unfortunately, once an individual undergoes a diminution in the ability of the immune system to respond to specific infectious processes, then there is a propensity for developing multiple infections, and thus each new sign or symptom has to be evaluated independently of prior symptom complexes. This possibility for serial infections, sometimes with multiple agents, tends to make the medical management of individuals with HIV infection particularly labor-intensive and costly. The clinician must always

balance the aggressiveness of the clinical workup against appropriate therapeutic options for individuals with the AIDS-related complex, but more often than not, it is desirable to proceed with the latest diagnostic tests, since isolation of specific organisms or the definition of specific clinical conditions can lead to appropriate therapy and may result in an improved quality of life for the patient.

The opportunistic infections that individuals develop with AIDS may be due to organisms that are ubiquitous in a specific environment, so that *Pneumocystis carinii* pneumonia is much more common in North America and Europe than in Africa, whereas cryptococcal meningitis and *Isospora belli* enteritis are much more common there. Other opportunistic infections represent reactivation of chronic latent viruses that may have been acquired at earlier ages as the result of intimate contact, such as herpes simplex, cytomegalovirus, and Epstein-Barr virus. However, in individuals with AIDS and severe immunodeficiency due to HIV, these viruses may reactivate in particularly virulent forms, so that chronic, persistent perianal ulcerations may be due to herpes simplex,[23] or cytomegalovirus may result in colitis, blindness, or a refractory pneumonia, syndromes associated with this virus which are seen only in severely debilitated hosts.[24] One conundrum in individuals with AIDS is that with appropriate medical technology, most of these

Table 2

Opportunistic Infections Indicative of a Defect in Cellular Immune Function Associated with AIDS

A. Helminthic Infection

1. Strongyloidiasis (disseminated beyond the gastrointestinal tract)*

B. Protozoan Infection

1. *Pneumocystis carinii* pneumonia
2. Disseminated toxoplasmosis, or toxoplasma encephalitis, excluding congenital infection
3. Chronic cryptosporidium enteritis (> 1 month)
4. Chronic *Isospora belli* enteritis (> 1 month)

C. Fungal Infection

1. Candida esophagitis, bronchopulmonary candidiasis*
2. Cryptococcal meningitis, or disseminated infection
3. Disseminated histoplasmosis*

D. Bacterial Infection

1. Disseminated (not just pulmonary or lymphatic) *M. avium-intracellulare* or *M. kansasii*
2. Extrapulmonary tuberculosis*

E. Noncongenital Viral Infection

1. Chronic (> 1 month) mucocutaneous herpes simplex
2. Histologically evident cytomegalovirus infection, including liver or lymph node
3. Progressive multifocal leukencephalopathy

*Not listed in original CDC definition of AIDS but subsequently added.

Table 3

Opportunistic Malignancies Indicative of a Defect in Cellular Immune Function Associated with AIDS

Neoplasm
1. Kaposi's sarcoma (in a person less than sixty years old)
2. High-grade, B-cell non-Hodgkin's lymphoma*
A. Burkitt's lymphoma
B. Undifferentiated non-Hodgkin's lymphoma, immunoblastic sarcoma
3. Primary brain lymphoma

*Not listed in original CDC definition of AIDS but subsequently added.

opportunistic infections or neoplasms can be diagnosed, and most of them can be treated. However, the recurrent succession of these debilitating diseases is analogous to the Hydra monster of Greek mythology, which grew back two heads for every one that was cut off. It is this succession of diseases that causes the ultimate mortality from AIDS.

The problem for the patient, the clinician, and society at large is how to determine when the diminishing returns of each new intervention mandate a less thorough investigation of the cause of new complaints. Although individuals who have had their third episode of *Pneumocystis carinii* pneumonia are much less likely to survive than those who have had their first, this kind of information only gives probablistic odds, and does not address the question for each individual of whether life extension at specific junctures promotes human dignity or human suffering.

Infection with HIV may result in neurological disease after initial seroconversion but more often manifests itself later in the course of HIV infection, though specific neurological sequelae may be seen at any point in time.[25] The most dramatic findings include dementia, encephalopathy, and neuropathies, which may involve either muscles or sensation, or both, as well as involvement of the spinal cord.[26, 27] Individuals with HIV infection may be more anxious or depressed, or both, because of the knowledge of their status and because of the social stresses attendant upon being a member of a high-risk group and carrying a life-threatening virus, but independent of these other behavioral modifiers, HIV infection may alter psychological and neurological functions early in the course of the illness. Thus, health care planners must integrate the psychosocial and neuro-behavioral needs of individuals with HIV infection in the calculations of the societal costs of infection, which have thus far been estimated to add as much as $8 billion to $16 billion to the cost of health care in the United States by 1991.[28]

Immature immune systems appear to be even more susceptible to the ravages of HIV infection, presumably because there are no immunologic reserves that have developed over several decades of successfully fending off environmental challenges.[29] Although a consensus among experts does not exist regarding the frequency with which offspring of HIV-infected mothers will be infected themselves, there is general agreement that it is a substantial figure, possibly the majority of live births.[30] These children may be born to mothers who are addicted to drugs or are from disadvantaged socioeconomic environments, or both, and who have to cope with their own HIV infections with all those associated medical problems. Children born with HIV infection may encounter difficulties in placement if their mothers and families are unable to care for them. Thus, the problem of

pediatric AIDS, which has grown rapidly in several major metropolitan areas — particularly New York, northern New Jersey, and Miami — raises additional medical, sociological, and ethical concerns for the development of public policy.

Clinical Management Issues: Diagnostic Concerns

The first major clinical use of the HIV antibody test was for the purpose of screening donated blood in order to protect the blood supply.[31] In the first few years of the test's utilization, a wide-ranging public debate occurred in which some individuals were proponents of using the test to screen the entire population, or subgroups of the population, such as individuals seeking marriage licenses; health care professionals; and individuals entering hospitals or being prepared for major surgery. Opponents of these more liberal indications for use of the HIV antibody test pointed out that despite the test being progressively improved and despite the ability to utilize independent corroboration with other more sophisticated tests such as the Western blot, testing for antibodies still seemed to produce an unacceptably high number of false positives, particularly in low prevalence areas, even though the use of a corroborative test substantially reduces the number of false positives.[32, 33] Another concern voiced by opponents of large-scale testing of the general population was that even if all individuals identified as seropositive were truly infected with HIV, once they were identified as seropositive there would be no effective therapies available to offer them. They would have knowledge that they were at increased risk for AIDS and would be at risk for many types of discrimination if the information could not be absolutely protected, with no prospect for reversing their infection. However, over the past year, clinical studies indicate that AZT is efficacious in prolonging life in individuals with AIDS and AIDS-related symptoms,[34] raising new questions of when to test. At the present time, AZT has not been shown to be effective in preventing AIDS in asymptomatic HIV-seropositive individuals, but the studies that are currently under way to evaluate this possibility could radically alter the clinical indications for HIV antibody screening. If AZT or any other antiretroviral drug is shown to prevent immunocompromise in asymptomatic seropositives, the argument could run that proactive HIV testing would be useful so that more individuals could be diagnosed and treated before the onset of irreversible clinical disease.

The argument that the detection of early infection may help prevent subsequent spread into the general population and may reduce morbidity has been the basis for much of current public health policy with regard to other sexually transmitted diseases. Since at the present time AZT looks promising but has not yet been shown to be effective for treating asymptomatic persons, there is much turmoil regarding this issue. Up to one-third of persons with AIDS or ARC who take AZT for more than several months have needed repeated transfusions, and there are those who feel that AZT is a highly toxic drug. Since the data suggest that individuals with lesser degrees of immunocompromise may tolerate the drug better, some rationale exists for earlier treatment. However, one does not know whether HIV could become resistant to AZT over long periods of time, since the drug only suppresses the virus's ability to replicate, and does not kill the virus or remove it from the body; other chronic viruses (for example, herpes simplex) can develop resistance to suppressive therapeutic agents.

Other clinical indications for the knowledge of an individual's HIV and immunologic status are emerging. For example, in children, the use of live virus vaccines, even though the organisms utilized in the vaccines are avirulent, could result in an HIV-infected im-

munocompromised child becoming very ill with a disseminated viral infection that the vaccine was designed to avoid. Family members may be in high-risk groups themselves and could be susceptible to serious infections from viruses that were excreted by asymptomatic children who had been recently vaccinated. Thus, the public is left with a fairly volatile situation, in which no proven interventions have been shown to alter the natural history of HIV infection in asymptomatic individuals, though several interventions are on the horizon. Individuals who are infected with HIV may benefit from knowing about this if they are going to be exposed to new infectious agents; however, one must be cautionary in noting that these are theoretical concerns, not ones that are currently standard medical practice. It is clear that as the medical advances continue — and one can only hope that they proceed at a rapid pace — then HIV diagnostics will be increasingly more useful. The test itself will have more meaning for individuals when clinicians have something to offer them. In the meantime, the public debate about these issues should help to educate both policymakers and clinicians as to the need to be very clear in their own minds why they want individuals to be screened for HIV.

HIV screening's use as a tool for the modification of high-risk behaviors, and thereby as a tool to decrease the spread of the retrovirus, is one of the major reasons that policymakers have felt the screening should be more widely available. In a context of a program of intensive education about risk behaviors, HIV testing may be helpful for specific individuals. Yet it is difficult to generalize about the efficacy of HIV testing itself, since very few individuals undergo antibody testing without receiving some form of counseling, which may be more relevant to potential behavior changes.

The substantial changes in high-risk behaviors by the gay and bisexual men in one Boston study were similar whether individuals were antibody-positive or -negative and whether or not they knew their test results.[35] On the basis of studies in which individuals enter as volunteers, are given guarantees of confidentiality, and are not under scrutiny by public health officials, it is particularly hard to generalize about the effect of mandating that people know their HIV antibody test results. One can only wonder whether mandatory testing could serve merely to intensify the development of an underground that could be more refractory to the educational messages available in studies, community-based testing sites, and other institutions that offer the test without coercing individuals to participate. The maintenance of a dialogue between the patients and their providers can allow for mutually reinforcing decisions as to when it is appropriate to perform HIV testing and what kinds of support the patient will subsequently need in order to maintain safer sexual practices and to receive appropriate medical follow-up.

Therapeutic Concerns

Another major dilemma for clinicians taking care of individuals with AIDS and HIV infection relates to the pace of clinical trials. At the present time, most persons with HIV infection are not receiving medication to counteract the progressive immunocompromise associated with HIV. Most newly available drugs for treating HIV infection will be tested in the ATEUs and Clinical Studies Groups (CSGs), which are federally funded and centrally coordinated to perform multicenter clinical trials. A consortium of Harvard Medical School–affiliated hospitals (Massachusetts General, Beth Israel, New England Deaconess) is the only such treatment site in New England. The ATEUs have begun several protocols utilizing AZT and are planning more studies to look at newer antiretroviral drugs. Since the criteria for inclusion in a specific clinical study must be fairly rigid, and

since many individuals may fall between the cracks in terms of the progression of their specific problems, a large underground has already developed to procure medications from Mexico and overseas in order to give individuals with AIDS and symptomatic HIV infection the opportunity to make their own decisions about whether they would want to receive a specific drug. Of great concern to clinicians is the fact that treatment with the first two highly publicized agents (Suramin and HPA-23) which act against the HIV-specific enzyme, reverse transcriptase, turned out to be more toxic than the untreated HIV infections would have been. Thus, in the absence of meticulous basic research, individuals may become more impressed by the merchandising of purported panaceas and thereby expose themselves to potential harm. By the same rationale, early HIV testing may be useful because an individual may be at a better point to take action that can prevent a more rapid decline in immunologic function. Many clinicians are concerned that drugs may not be tested soon enough on less symptomatic, seropositive persons. Many asymptomatic individuals, perceiving themselves to be at increased risk for developing symptomatic HIV infection in the near future, are clamoring to receive AZT or other, less studied agents, and they indicate that they do not want to sit and wait while their immunologic function inexorably declines. If many of these minimally symptomatic individuals had taken HPA-23 or Suramin, they would have caused themselves more harm than benefit. Thus, the federal health authorities feel that in studying new and promising agents, they must balance the progressively increasing gravity of the epidemic against the need to conduct studies in a careful and organized fashion.

Many hopes have been raised regarding drugs besides AZT, such as Ribavirin, Ampligen, Phosphonoformate, and a host of other compounds.[36, 37, 38] Many of these drugs are now undergoing initial clinical trials, but the process can be a long and arduous one. First, investigators must develop a hypothesis as to why a specific agent may work in a test tube and must demonstrate the efficacy of the compound against HIV-infected cells. Initial studies in humans have to evaluate the pharmacokinetic properties of the drug as well as its toxicities. Then, studies have to show that in human beings a specific drug may have efficacy against HIV infection. The traditional investigational gold standard has been to test a candidate drug in humans against a placebo in a randomized, controlled fashion, utilizing subjects that are selected to be similar in terms of infection and disease characteristics. Many of the promising reports about agents other than AZT do not involve randomized, controlled trials and thus are often a series of anecdotes. The erratic nature of HIV infection makes noncontrolled trials difficult to interpret, since some individuals may remain asymptomatic for as long as nine years after HIV infection, while others may develop AIDS within a year after seroconversion. Individuals with Kaposi's sarcoma, in particular, constitute a subgroup that in the absence of opportunistic infections may remain quite well, with fairly intact immunologic function, for long periods of time.

The clinical end points that are used to evaluate the efficacy of particular therapies are still not standardized. If death is utilized as an end point, one has to follow a large cohort of individuals with fairly advanced HIV infection in order to establish an adequate difference between a new therapy and a placebo. This was done in the case of the trial of AZT, but the data in that study indicated that individuals who had ARC tended to benefit more from AZT than those with AIDS. This would suggest that AZT would be better utilized in individuals who might have earlier stages of HIV infection. However, the AZT trial in asymptomatic HIV-seropositive individuals may have to go on for at least three years before it can be established whether treatment with AZT has a sufficiently large protective effect to warrant the toxicities that may be encountered in the course of therapy. If one

does not use death as an end point, but rather opportunistic infections, the cohort size must still be large and homogeneous at the outset in order to produce meaningful data that can establish the efficacy of a specific agent. The clinical and laboratory criteria, which are needed to include individuals in specific cohorts and to assess the effectiveness of specific agents, have not yet been routinely standardized. For example, some individuals feel that the presence of thrush is a particularly bad prognostic sign,[39] whereas others are more concerned by the persistence of constitutional symptoms. It is not clear whether one can compare an asymptomatic person with thrush to a person who has lost significant weight and who has persistent fevers, chills, and sweats and multiple hematologic abnormalities. In the lab, the most useful immunologic criterion for inclusion in a specific group that would be evaluated in a drug trial would be the absolute T-helper lymphocyte number.[40] This has been shown to be useful in epidemiological studies, but whether improvement or stabilization in this parameter is the best predictor of chemotherapeutic efficacy is still an open question. Several virologic parameters may be epidemiologically useful as well, but further study is required as to their usefulness as prognostic markers after individuals undergo antiretroviral chemotherapy. Patients who have positive cultures for HIV or who have been shown to have HIV antigen in their serum (patients may be antigenemic and not viremic) tend to be more likely to become clinically ill over short periods of time.[41, 42] However, the reversal of antigenemia or the inability to culture virus after an individual has been treated with a drug may not ipso facto mean that the drug is highly effective. These parameters are undergoing careful study and will increasingly become useful in characterizing stages of HIV infection, but the highly individualized responses to infection with the retrovirus mean that it is still very hard to establish a typology that would allow clinicians to give short trials of therapeutic agents and utilize surrogate markers as a means for proving drug efficacy. In summary, in the short run there will be no quick answers as to which drugs are the most effective; rather, ongoing studies of natural history will be necessary, unless novel agents are developed which prove to be highly effective in altering or reversing the HIV-induced immunodeficiency and its sequelae.

The need for long-term, prospective, careful studies of individuals, utilizing placebos and careful controls, is clear-cut. Yet, given the magnitude of human suffering engendered by HIV infection, many clinicians feel that an academic approach is unacceptable. Some individuals have felt that historical controls can be used to establish baseline rates of progression in the natural history of HIV infection and that these can be compared to individuals who are treated with specific regimens. The problem with using historical controls is that as the epidemic evolves, there are changes in the natural history of HIV infection which have been unanticipated. Thus, comparisons of people who were infected with HIV several years ago with those who are undergoing therapeutic regimens now may lead to skewed interpretations. For example, at the outset of the epidemic, almost one-third of individuals who were initially diagnosed using the CDC definition of AIDS had Kaposi's sarcoma, whereas at the present time less than one-fifth of the new cases carry this diagnosis. It is unknown whether the decreased incidence of Kaposi's sarcoma reflects changes in behavior, changes in certain biological cofactors (such as the use of volatile nitrites, or "poppers"), or decreased transmission of another viral cofactor.

The vagaries of the natural history of HIV have complicated the need for expeditious clinical trials, and appropriate clinical concerns have been perceived by some segments of the population as an insensitivity. This has led to the burgeoning of the therapeutic underground and to an increased alienation from clinical investigators among some HIV-in-

fected persons. Occasionally, individuals who have participated in randomized trials have gone so far as to utilize drug-analysis laboratories in order to assess whether they are receiving a placebo, and have either dropped out of trials or have supplemented their regimens with nonprotocol drugs because of their sense of urgency regarding treatment. These anecdotes reflect the exceptions rather than the rule, but they underscore the highly charged environment that is evolving in this time of uncertainty. Individual self-medication has the potential to create serious therapeutic problems, since if every individual who were HIV-infected were to experiment with different types of drugs, the results that might be obtained in specific clinical trials would be difficult to interpret. But many seropositive persons are uncomfortable not knowing whether they have received a placebo. The increased availability of AZT and the lack of a standard, accepted criterion by all clinicians in prescribing the drug create the potential to exacerbate this situation further. At the present time, it is known only that individuals who have had one episode of *Pneumocystis carinii* pneumonia or who have constitutional symptoms and other ARC-like manifestations have had their lives extended by taking AZT. However, many HIV-infected individuals who have either minor opportunistic infections, such as thrush or zoster, or asymptomatic depressions in their T-helper lymphocyte count, or both, are electing to take AZT. In the absence of clear-cut data and through the process of extrapolating from the clinical trials of sicker individuals, they prefer risking the potential toxicities of AZT to waiting until it is clearly shown that taking the drug at earlier stages of infection is useful. Blanket statements saying that individuals must either be in clinical trials or not take medication are not realistic in the current climate. On the other hand, if everybody did exactly as they pleased, utilizing any available drugs through the black market, further knowledge about the efficacy of antriretroviral therapy could be critically delayed or limited. There are no easy or glib answers. An ongoing dialogue among researchers, clinical providers, and the communities at risk for HIV infection must continue, in order to address these highly urgent human needs in a responsible fashion. Yet an adequate level of scientific rigor must also be maintained so that these crucial questions can be answered as rapidly as possible.

Up until now, clinical trials have tended to look for the magic bullet, that is, a single drug that will attenuate the effects of HIV infection. However, many researchers feel that this approach may be simplistic, since the individual with HIV infection faces two types of problems. Because the virus is immunosuppressive, the individual must have his or her immune system restored if the onset of opportunistic infections or malignancy is to be avoided. At the same time, the retrovirus itself must be inhibited from replicating in order to prevent the extension of the infection and subsequent further immunosuppression.[43, 44] Some of the first drugs to treat HIV infection were stimulators of the immune system, such as interferon and interleukin-2.[45] Whereas they tended to increase the numbers of lymphocytes which could potentially fight infection, they also tended to enhance the ability of HIV to replicate, thus abetting infection, and were ultimately not successful by themselves. Drugs like AZT inhibit specific enzymes of the virus and prevent it from multiplying, but do not restore the immune system by themselves. Thus, the possibility exists that combined chemotherapy with an immunostimulatory drug and a drug that acts specifically against the virus could be a major answer in treating individuals with HIV infection and preventing further immunologic compromise.[46] However, in order to assess adequately the potential toxicities of individual agents, such trials would have to be performed serially; in other words, the effects of either drug by itself would first have to be assessed, and only then could the drugs be studied in combination. Thus, some ap-

proaches offer much promise, but even more time may be required to study them in a responsible fashion, thus further straining the patience of individuals who are at risk for immunologic compromise. Some feel that although serial trials of these drugs represent a scientifically worthwhile approach, so many individuals could clinically deteriorate before definite data were collected that combination studies should begin in a more expeditious fashion. Previous medical experience shows, however, that when two drugs are given together, unexpected synergistic toxicities supervene instead of synergistic therapeutic effects. Dual therapy may result in lessened therapeutic efficacy of either drug alone (antagonism) in vivo even if in vitro data look promising. Thus, the dialogue between the affected individuals and the research community must take each side into account. The old dictum, Primum non noce (First do no harm), must be balanced against the problem that can result from too much delay in initiating a promising therapeutic regimen. The only answer is constant questioning and dialogue in order to expedite the process of making useful combination treatments available, without rushing to judgment in such a way that more individuals are harmed because of inadequate antecedent study.

Care-Related Issues

The AIDS epidemic raises many issues regarding the optimal delivery of services to individuals infected with HIV who subsequently develop problems related to immunocompromise. Although persons with AIDS have a markedly shortened life expectancy, they can respond well to specific treatment regimens, particularly after their first episodes of opportunistic infection. The initial approach toward the management of patients with HIV infection tended to be technologically intensive, and led to patients being hospitalized for longer periods of time. The model developed in San Francisco is one that optimally utilizes outpatient resources and maximizes home care and treatment in the ambulatory setting. Unfortunately, the ways in which health care is financed in many areas tend to create disincentives for early discharge and the provision of comprehensive outpatient services. This will become increasingly penny-wise and pound-foolish, given the availability of prophylactic regimens that require some level of medical expertise, such as the administration of aerosolized Pentamidine in order to prevent the recurrence of *Pneumocystis carinii* pneumonia. Health care planners and policymakers will need to continually talk to clinicians, patients, and advocacy groups for individuals at high risk for HIV infection in order to create the most satisfactory approaches to caring for individuals in community settings, which may provide a less depressing environment and which certainly provide a less costly one. In order for these novel programs to be successful, there must be a comprehensive set of supports which includes a wide range of health care providers, including home health aides, nursing assistants, physical and occupational rehabilitation specialists, nutritionists, and mental-health-care workers, so that the deinstitutionalized patients do not return to tertiary institutions with more complicated medical problems that could have been anticipated had the appropriate interventions been instituted earlier. Health care providers such as physicians and nurses need to increasingly become aware that many of the individuals at highest risk for HIV infection do not come from "traditional" social environments. The effectiveness of the health care team can only be enhanced if providers recognize the validity of same-sex spouses, nonnuclear family units, and nonmedical resources in communities that comprise sexual, cultural, and racial minorities. Since so much of HIV infection relates to behavioral issues, providers must

educate themselves about alternative lifestyles and must understand how critical it is that they relate to clients as nonjudgmental care givers and educators.

HIV infection results in problems that involve the whole patient, who is the sum total of many parts greater than individual subspeciality concerns. Therefore, patients who are infected with the retrovirus need to be approached clinically by a multidisciplinary team of health care providers. This team must include subspecialists in areas of expertise such as infectious diseases, hematology, oncology, pulmonary diseases, gastroenterology, and often a host of other subspecialities. However, these patients have a great need to have their care integrated; thus, there will be a continuing need for primary care generalists to serve as their gateway to the health care system. In some university hospital settings, infectious disease specialists tend to be the primary providers of care for individuals with symptomatic HIV infection, but in others, general internists and family practitioners have done a fine job and have tended to be the health care providers who oversee the series of consultations that may be necessary in the course of HIV infection for any given individual. The health care team can be greatly enhanced by the inclusion of nurse practitioners and physicians' assistants who have developed specific skills around AIDS and HIV infection, since individuals with these problems may need a great deal of education, moral support, and clinical monitoring that do not necessitate the constant involvement of the subspecialist. In addition, the ongoing involvement of mental health professionals ranging from neurologists to social workers can greatly enhance the ability of individuals with HIV infection to function well in society. Not every individual with HIV infection will invariably need to see the psychiatrist or the gastroenterologist, but it is important to develop a referral network that will allow for a rational pattern of integrated health care for each individual who is diagnosed with HIV infection and its attendant clinical sequelae.

Infection Control

The last major policy issue regarding HIV infection relates to infection control. As with so many other aspects of the AIDS epidemic, the public dialogue on this issue has tended to careen between hysteria and apathy, whereas the most appropriate course is one of prudent caution based on the well-documented epidemiology of retroviral infection. The precautions that providers need to take regarding HIV infection are virtually identical to those which are taken with respect to any bloodborne disease and have been recently well described by the Centers for Disease Control.[47] One must add the caveat that individuals who are infected with HIV may be more susceptible to certain types of infections — for example, tuberculosis — that may in and of themselves be contagious to individuals with intact immune systems. Therefore, clinicians need to respond with the appropriate thoughtful caution in the care of individuals with HIV infection. Thus, if an individual who has HIV infection has an atypical chest x-ray and is coughing, it behooves the provider to suggest that the patient be placed on respiratory isolation until the diagnosis of tuberculosis is excluded. However, irrational infection control procedures serve only to stigmatize the individual, give a false sense of security to staff members, and lead to suboptimal, alienated medical care.

Traditional practice has included the documentation in the medical record of all information that could possibly be of clinical importance, on the presumption that no clinician's memory is infallible and that others may benefit from this documentation in the future. However, antidiscrimination provisions against individuals with HIV infection

are lacking in most jurisdictions, and since, particularly in small medical settings, it is very difficult to keep medical information inviolate, individuals may be at risk from external social sanction if their HIV status is documented. Therefore, many have felt that information about persons with HIV infection should never be placed in the medical record. However, where HIV-related information has been obtained in a noncoercive fashion and where knowledge of this information on the part of other members of the health care team may be important for patient management, it seems that discussion should focus not on the compromise of medical care, but on how best to protect individuals from capricious or inappropriate disclosure and subsequent discrimination. Therapeutic interventions available for HIV-infected individuals, it is hoped, will continue to increase over the next few years, and as they do, the likelihood will also grow that within the health care system more individuals will be disclosed as HIV-infected. In order to avoid further exacerbation of the patients' need for comprehensive medical care, which may necessitate documentation of their clinical status, legislation that addresses the just concerns of patients is urgently needed. Discussions among medical providers, those who make public policy, and the general public must lead to a resolution that creates an environment in which individuals will not be stigmatized in the process of seeking health care.

With more than one million HIV-infected persons in the United States, any actions that potentiate alienation from the health care system and impede education around risk reduction are inappropriate. In the midst of this distressing epidemic, all of us — researchers, providers, patients, and the public — face the great challenge of having to rapidly assimilate new technical information while remodeling the anachronistic social systems that tend to increase the underlying anxieties. Until we have definitive therapeutics and chemoprophylaxis, these anxieties will persist.

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Glossary continued from page 36

Immunocompromise. Alterations in immune function which are suggestive of a decreased ability to fight off infections and the development of malignancies.

Immunoregulation. The processes by which the body is able to prevent immunocompromise.

Immunostimulation. The process by which substances turn on specific parts of the immune system.

In vitro. Experiments that occur in artificial laboratory environments outside the living body.

In vivo. Experiments that occur in the living organism, either using animal models or clinical studies that take place in humans.

Maculopapular. A rash that is reddened, with some irregular raised surfaces.

Neurological syndrome. Any process that results in an alteration of the nervous system. This can result in confusion, coma, muscle weakness, strange sensations, or any combination of these.

Neuropathy. Any process that impairs the functioning of specific nerves.

Opportunistic infections/ neoplasms. Infectious diseases or tumors that develop because of a weakening of the immune system, so that processes which are usually quite innocuous take advantage of the resultant immunocompromised state.

Persistent generalized lymphadenopathy (PGL). Swollen glands in more than one noncontiguous site throughout the body which stay enlarged for at least three months.

Synergism. Any combination that results in a multiplicative effect rather than an additive effect.

T-helper lymphocyte. A type of white blood cell that is responsible for orchestrating many of the interactions of different, other blood cells in the immune system. This is one of the cell types that become particularly affected by HIV, and the T-helper lymphocyte count can be a useful marker in following the progress of HIV infection in specific individuals.

Thrush. A yeast infection of the tongue.

Zoster. Reactivation of the chicken pox virus, also known as shingles. This usually results in a painful band either on the trunk or on the face, with painful blisters.

"I don't consider myself a person who's dying from AIDS. I certainly consider myself a person who's been living with AIDS. I don't consider myself an AIDS victim, and I really wish people in the media would stop using that terminology. I think that's one of the most damning things that you can say about a person, is that they're just a victim, and I think that part of the way I've come to look at this is that I'm a person who's still in control of my life and I refuse to be victimized by AIDS or anyone who's connected with this disease in any way. I maintain control."

Glossary

Candida esophagitis.	Yeastlike fungus infection of the esophagus.
Hepatitis B.	Viral infection whereby a small virus attacks the liver, often producing jaundice.
Hyperallergenic subjects.	People who have heightened allergic responses.
Persistent generalized lymphadenopathy (PGL).	Persistent inflammation of the lymph nodes, particularly the axilla and groin, in response to an infection.
Transplacental or placental spread.	Transmission of the virus from the bloodstream of the mother to the blood of the unborn baby.