AIDS; HIV Infection
Natural History and Some Implications

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I. In accordance with information available to date, the following outline presents the natural history of infection with the human immunodeficiency virus (HIV). Also see the diagram.

A. Investigators currently believe that once infected with HIV, an individual remains permanently HIV infected and infective.

B. WINDOW PERIOD:

1. If one considers the incident during which HIV infection occurs as representing zero time, a febrile, mononucleosis-like syndrome may occur at or shortly after zero time and lasts 3-14 days.

2. Seroconversion (the change of the patient's serum from negative reactivity for serum HIV antibodies to positive reactivity for such antibodies*) typically occurs 6-12 weeks after zero time but may take as long as 6 months to occur.**

* As Zolla-Pazner13 has reported, the "serologic test for the antibody to HIV [positive ELISAs confirmed by a positive Western blot test] is the only specific test for [HIV] and the development of an immune response to it. The presence of antibody gives no information about the extent of [HIV infection]."

** An acute meningitis can occur at the time of seroconversion and indicates that HIV can cause central nervous system illness relatively early in the course of HIV infection.

3. The interval of time between zero time and the point of seroconversion is termed the WINDOW PERIOD:

a. During this span of time, the individual is both HIV infected and HIV infective but not yet seropositive (serum HIV antibody positive) and therefore generally not yet diagnosable as having HIV infection.*

b. During this window period, the individual is asymptomatic except for the mononucleosis-like, acute viral syndrome (see

Cultures for HIV from such patients may be positive, but the culture techniques are expensive, time-consuming and not routinely available in clinical diagnostic virology laboratories and currently yield only a 60-90 percent response to the question: "Is the virus present or not in the body fluids examined?" One can now spend $300-$500 and not obtain an unqualified answer to that question.

* Investigators have recently developed an enzyme immunoassay that detects HIV core antigen (HIV-Ag) in serum. Initial observations suggest an inverse relationship between the detection of HIV-Ag and serum HIV antibodies to the p24 HIV core antigen. Serum HIV-Ag detection has the potential for a rapid diagnostic test for HIV infection before the development of detectable serum HIV antibodies (and during the initial, mononucleosis-like syndrome of HIV infection).

Later in the course of HIV infection, as detectable antibodies to the p24 HIV core antigen and the gp41 HIV envelope antigen first develop (at the point of seroconversion), the concentration of HIV-Ag falls, and the patient may become HIV-Ag negative. Antibodies to gp41 appear to be detectable before antibodies to p24 and may overlap the presence of HIV antigen. The apparent sequence in the appearance of markers is HIV-Ag, antibody to envelope (gp41) antigen, and antibody to core (p24) antigen.

Then, as HIV infection progresses (during the latent period, for which see the discussion below, and beyond the latent period), the concentration of core antigen again rises. The presence of antigen in the serum of chronically HIV infected individuals appears related to severe immunodeficiency. Investigators recently reported that the mean HIV-Ag level fell in patients treated with azidothymidine (AZT). Thus, increases in the concentration of core antigen may correlate with clinical deterioration.

However, tests for HIV-Ag are still in an experimental stage and are not generally available for insurance testing procedures.
NATURAL HISTORY OF HIV INFECTION

WINDOW PERIOD
(Duration 6-12 weeks)

LATENT ASYMPTOMATIC PERIOD

SYMPTOMATIC PERIOD

INCEPTION OF HIV INFECTION

ZERO TIME

MONONUCLEOSIS-LIKE SYNDROME

DURATION 3-14 DAYS

SEROCONVERSION

OVERALL MORTALITY 20% WITHIN 5 YEARS

IMMUNE SYSTEM IMPAIRED

TIME OF OCCURRENCE VARIABLE; PROGRESSION OF IMPAIRMENT VARIABLE

IMMUNE SYSTEM NOT IMPAIRED

DURATION?

REMAINS WITH IMPAIRED IMMUNE SYSTEM; REMAINS ASYMPTOMATIC

PROGNOSIS?

REMAINS WITH NORMAL IMMUNE SYSTEM; REMAINS ASYMPTOMATIC

PROGNOSIS?

SYMPTOMS WHICH DO NOT FULFILL CDC CRITERIA FOR AIDS

ESTIMATED INCIDENCE 5-10 TIMES THE INCIDENCE OF AIDS

AIDS

PROGNOSIS?

AIDS

PROGNOSIS?

DEATH

DEATH

HIV—Human Immunodeficiency Virus
AIDS—Acquired Immunodeficiency Syndrome
section I-B-1) and the acute meningitis that can occur at the time of seroconversion (see section I-B-2).

c. An early response to HIV infection is significant T8-cell elevation while the number of T4-cells remains relatively constant.* This elevation is the normal, early response of the immunologic system to many infections and may occur during the initial, mononucleosis-like syndrome that follows the inception of HIV infection. As with most viral infections, the T8-cell count restabilizes after the initial HIV infection, and the restabilization may take several months. In many individuals sero-positive for HIV, the T8-cell count then remains normal for prolonged periods.

* The increased T8-cell count may cause an inversion of the T4/T8 ratio, but such a change has a different implication prognostically than an inversion of the T4/T8 ratio due to a decreased T4-cell count (see the relevant portions of section I-C).

d. Serologic testing may be misleading in the first 15 months of life:

i. Cord blood antibodies are of maternal origin; usually disappear by the age of 3-6 months; and rarely persist for 15 months.

ii. In infected children, a serum HIV antibody negative “window period” may stretch beyond the first year of life.

C. LATENT PERIOD: A latent, asymptomatic period follows seroconversion, and this period is of variable duration. This period may be so short as to be practically non-existent, or it may last indefinitely. HIV infected individuals remain asymptomatic throughout this time.

During this period, the HIV infection may remain immunologically quiescent and not affect the body's immunologic system, or the infection may progress to impair the body's immunologic system (while the individual remains asymptomatic). If impairment occurs, clinical alterations reflecting the resultant immunologic dysfunction may appear, and the insurance industry has considered these alterations to be substitute markers for HIV infection. These substitute markers are therefore later occurring markers for HIV infection than the presence of serum HIV antibodies; appear less consistently with HIV infection than serum HIV antibodies; and are therefore less suitable markers for HIV infection than serum HIV antibodies.

1. Some of the substitute markers:

a. Decreased absolute T4-cell count with a resultant inversion of the T4/T8 ratio.* The absolute numbers of total lymphocytes and T8-cells may also fall, but the fall is proportionately greater for the T4-cells than for the T8-cells. Some investigators believe that an absolute number of T4-cells below 400/cu mm may be the most significant T-cell data.

T4-cells are the key to the body's immunologic system to the degree that any infection, physiologic state or drug that alters the function of T4-cells in turn affects the functioning of the entire immunologic system. Entrance of HIV into T4-cells is the major route for HIV infection. When that occurs, a vast majority of the infected T4-cells dies, and a majority of the T4-cells that remain becomes functionally impaired. As the T4-cells are destroyed or functionally impaired, the immunologic defenses of the host (the infected patient) are similarly destroyed or impaired resulting in (i) a multitude of opportunistic infections of increasing severity and/or (ii) various malignancies.

b. Increased beta-2-microglobulin (B-2-m) level*

c. Increased immunoglobulin (lg) levels, most commonly IgG and/or IgA

d. Absolute lymphopenia

e. Thrombocytopenia

f. Increased neopterin level

* The substitute markers currently used by the insurance industry.

2. As noted, the appearance of the substitute markers announces the progression of pre-existent HIV infection to the point at which the body's immunologic function has deteriorated. The markers reflect immunologic dysfunction. But conditions other than HIV infection can cause immunologic dysfunction. These substitute markers are therefore less specific for HIV infection than the presence of serum HIV
antibodies, and this deficiency is another reason that the substitute markers are less suitable markers for HIV infection than serum HIV antibodies.

a. An inverted T4/T8 ratio can appear in a variety of viral diseases including acute infectious mononucleosis. Abnormalities in the T4/T8 ratio, particularly those due to elevations in the T8-cell count, are characteristic ally associated with the acute, chronic or recurrent viral infections (particularly those caused by the herpes group of viruses) that are common in sexually promiscuous people.

b. B-2-m is present in high concentrations in a variety of diseases including a number of B-cell malignancies, autoimmune diseases, diseases associated with chronic inflammation, and acute viral infections (including infectious mononucleosis and viral hepatitis). B-2-m is eliminated by the kidneys, and abnormally elevated serum B-2-m concentrations have therefore been reported in renal failure.

c. Neopterin levels may be elevated in cancer, viral infections, allograft rejections and tuberculosis.

3. According to some reports, increasing degrees of abnormality for some of the substitute markers (decreased absolute T4-cell counts, inverted T4/T8 ratios due to disproportionately decreased T4-cell counts, increased B-2-m levels, increased immunoglobulin levels) which reflect immunologic dysfunction are directly related to increasing likelihood of progression of HIV infection during the asymptomatic, latent period to the full-blown, clinical acquired immunodeficiency syndrome (AIDS) as currently defined by the centers for Disease Control (CDC).*

* The CDC has recently revised its surveillance case definition for AIDS. The revision was published in a supplement to the August 14, 1987 issue (volume 36, number 15) of the CDC's Morbidity and Mortality Weekly Report (MMWR).

D. SYMPTOMATIC PERIOD: After a variable period of latency (which can be very short-lived or very prolonged), symptoms may appear. The symptoms may or may not fulfill the current CDC criteria for the diagnosis of AIDS. Stated differently, AIDS is the final expression of a disease process that apparently also exists clinically in other symptomatic forms such as persistent, generalized lymphadenopathy (PGL) and those symptomatic states which do not fulfill the current CEC criteria for the diagnosis of AIDS.

1. Investigators have estimated that for every patient with AIDS as defined by the CDC, 5-10 patients have symptomatic HIV infection with symptoms which do not fulfill the CDC’s diagnostic criteria for AIDS.

2. Investigators have reported that HIV antibodies may decline as clinical AIDS becomes more severe and that patients with very advanced disease and nearly total ablation of the immunologic system may lose their detectable serum HIV antibodies terminally.

II. The statements in this memorandum can be summarized by observing that the current, accepted test procedure for detecting HIV antibodies (repeatedly positive ELISAs confirmed by a positive Western blot test) identifies exposure to HIV AND the presence of HIV antibodies in the individual tested and does not identify the presence of AIDS or any of its related diseases in the individual tested or guarantee that the HIV infected individual will develop AIDS or any of its related diseases. However, the ability to detect HIV infection (by appropriate tests for HIV antibody) as soon as possible after HIV infection occurs is valuable to us as underwriters because of the following group considerations (characteristics statistically defining the group to which the individual belongs; the group experience):

A. The following incidences of clinical AIDS have been reported to the CDC by AGE GROUPS from early 1981 to 2/2/87:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percent of Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 13 yrs</td>
<td>1</td>
</tr>
<tr>
<td>13-19</td>
<td>0</td>
</tr>
<tr>
<td>20-29</td>
<td>21</td>
</tr>
<tr>
<td>30-39</td>
<td>47</td>
</tr>
<tr>
<td>40-49</td>
<td>21</td>
</tr>
<tr>
<td>over 49</td>
<td>10</td>
</tr>
</tbody>
</table>

Thus, 68 percent of the total cases of AIDS reported from early 1981 to 2/2/87 were in the age range, 20-39 years, and 89 percent of the total cases reported during the same time span were in the age
range, 20-49 years. At ages over 60 years, infection rates are so low that they may be ignored for practical purposes.

B. The accepted test procedure (repeatedly positive ELISAs confirmed by a positive Western blot test) for detecting HIV antibodies has been reported to have an estimated false positivity rate of only 0.15 percent\textsuperscript{11} although other investigators have reported even lower estimated rates (0.01 and 0.005 percent) in populations with low risks for HIV infection.\textsuperscript{10}

C. Investigators have estimated that 20-30 percent of HIV infected individuals progress to symptomatic, clinical AIDS within 5 years following inception of HIV infection. These rates increase with the passage of additional time. The greatest risk factor for progression of HIV infection to clinical AIDS is time. The risk of progression to AIDS is greater during the second five years of HIV infection. Indeed, both the CDC and the U.S. Surgeon General have supported what has been becoming the prevailing medical view: the vast majority of HIV infected individuals will ultimately progress to a more serious stage of the disease and succumb to its complications.

D. The overall mortality rate among asymptomatic, serum HIV antibody positive individuals is 20 percent within 5 years.\textsuperscript{11} Based on the 1975-80 Select Basic Tables for Males, this figure is equivalent to substandard anticipated mortality rates of 6200 percent for 27-year-old males, 3900 percent for 37-year-old males, and 1600 percent for 47-year-old males (see the table in section II-G).

\* Walter A. Hoskins reported a statistical analysis of mortality from HIV infection based on the Frankfort study of progression rates of HIV infection and the CDC mortality rates of AIDS. Hoskins calculated a cumulative mortality rate of 18.6 percent at 5 years following inception of HIV infection (not inception of symptomatic, clinical AIDS).\textsuperscript{4}

E. The average survival time for individuals with diagnosed AIDS has been reported to be 13 months.\textsuperscript{13} Michael J. Cowell reported a calculated "life expectancy of about 2.1 years [from inception of clinical AIDS] and an 8-year AIDS [not HIV infection] survival rate of 4.7 percent."\textsuperscript{4}

Note the median survival times for AIDS with the following specific clinical presentations:

1. 4-5 months after the onset of OPPORTUNISTIC INFECTIONS; and

3. 17-18 months after the diagnosis of KAPOSI's SARCOMA has been made.

F. Projections:

\begin{tabular}{|c|c|}
\hline
1. Cumulative cases of AIDS reported by end of year, U.S.A. & 1986 \hspace{1cm} 35,000 & 1991 \hspace{1cm} 324,000 \\
\hline
2. Estimated number with HIV infection, U.S.A. & 1-2 million & 5-10 million \\
\hline
\end{tabular}

G. The age distribution reported in section II-A is significant to the insurance industry because of the following considerations:

1. The younger-aged, medically unimpaired life insurance clients have, of course, lower anticipated group mortality rates than the older-aged, similarly medically unimpaired clients. But, when burdened with HIV infection, the younger-aged must face anticipated group mortality rates far exceeding the rates anticipated for even the much older but medically unimpaired.

a. As concrete examples, note the following lifedata for large groups of medically unimpaired males and large groups of asymptomatic, HIV antibody positive (Ab +) males at the ages listed. The calculations assumed the same overall survival rate, 80 percent in 5 years, for asymptomatic, serum HIV antibody positive individuals at all ages (see section II-D).

\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
age & 5-year survival rate reported as percentage of reported standard mortality & 5-year survival rate reported as percentage of reported standard mortality & expected average yrs of survival for GROUP at age listed & underwriting rating as percentage of standard mortality & underwriting rating as percentage of standard mortality \\
\hline
22 & (1) & (2) & (3) & (4) & (5) & (6) \\
22 & 99 & 80 & 54 & 15 & 100 & 5400 \\
27 & 99 & 80 & 49 & 12 & 100 & 6200 \\
32 & 99 & 80 & 44 & 11 & 100 & 5400 \\
37 & 99 & 80 & 40 & 10 & 100 & 3900 \\
42 & 99 & 80 & 35 & 10 & 100 & 2500 \\
47 & 98 & 80 & 31 & 10 & 100 & 1600 \\
\hline
\end{tabular}

Survival percentages and life expectancies are based on the 1975-80 Select Basic Tables for Males.
b. Note the following data from the table:

i. For each of the ages listed, the figures in column 4 are significantly lower than the figures in column 3 for the corresponding ages.

ii. For each of the ages listed, the figures in column 6 are significantly higher than the figures in column 5 for the corresponding ages.

iii. For each of the ages listed, the figures in column 6 are well over 550 percent anticipated mortality, the figure which the life insurance industry generally considers the highest anticipated mortality at which life insurance can be offered.

2. The insurance industry does not charge appropriately if groups of insured, younger-aged clients were to be burdened by the inclusion of HIV infected individuals with high mortality rates. To compensate for such a burden, the industry would have to ask the non-HIV infected insurance clients to share the resultant increased cost of claims and thereby deny the industry's commitment to charge clients their fair shares of the total risk.

References


