Perspectives on Retroviruses and the Etiologic Agent of AIDS

G.D. HSIUNG, Ph.D.

Virology Reference Laboratory, Veterans Administration Medical Center, West Haven, and Department of Laboratory Medicine, Yale University School of Medicine, New Haven, Connecticut

Received June 22, 1987

In 1911, the first retrovirus was described: the Rous sarcoma virus, an avian retrovirus. Forty years later the murine leukemic virus, a mouse retrovirus, was reported. Although many other retroviruses from non-primate species were identified during the 1960s, the first primate retrovirus was not recognized until it was isolated from a monkey tumor in 1970. The search for human retroviruses in human leukemic cells remained unsuccessful at that time.

Facilitated by the discovery of T-cell growth factor, a substance used for the propagation of human leukocytes in cultures, the first human retrovirus was discovered in 1980. Soon thereafter, in 1983, another human retrovirus, human immunodeficiency virus (HIV), was reported and implicated as the etiologic agent of AIDS. The isolation and identification of HIV has stimulated much interest in the study of human retroviruses and the control of this new viral disease.

HISTORICAL BACKGROUND

Retroviruses of Animals

Although the name retrovirus was not used at the time, the first retrovirus characterized was the Rous sarcoma virus which caused tumors in chickens [1]. Forty years later, Gross reported that an agent in cell-free extracts, now known to have been a retrovirus, could induce leukemia in infant mice [2]. The latter report initiated many subsequent studies on murine retroviruses, which have been reviewed elsewhere [3]. It was not until the 1960s that retroviruses of other species were discovered (refer to Table 1). These include the feline leukemia virus [4], the bovine leukemia virus [5], and many others from non-primate mammalian species [3,6]. The first non-human primate retrovirus identified was the Mason Pfizer monkey virus (MPMV) which was isolated from the mammary carcinoma of a rhesus monkey in 1970 [7]. In early studies, these retroviruses were recognized and identified by biological transmission and/or by morphological observation of virus particles in leukemic cells. Since retrovirus particles were easily found in the leukemic cells of chickens, mice [3,6], and guinea pigs [8], a number of investigators, including our own group at the West Haven VA Hospital, had examined, without success, numerous samples of human leukemic cells for human retroviruses. Therefore, it was postulated that human retroviruses might be present in an incomplete form in human tissue, thereby remaining undetectable by electron microscopy.

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Abbreviations: AIDS: acquired immune deficiency syndrome ARV: AIDS-associated retrovirus ELISA: enzyme-linked immunosorbent assay HIV: human immunodeficiency virus HLA: human leukocyte antigen HTLV: human T-cell lymphotropic virus IL-2: interleukin-2 LAV: lymphadenopathy-associated virus RT: reverse transcriptase enzyme TCGF: T-cell growth factor

Address reprint requests to: G.D. Hsiung, Ph.D., Director, Virology Reference Laboratory, Veterans Administration Medical Center, West Haven, CT 06516

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TABLE 1
Discovery of Retroviruses of Man and Animal*

| Date Reported | Name of Retrovirus                        | Investigator [Reference] |
|---------------|------------------------------------------|--------------------------|
| 1911          | Avian sarcoma virus                       | Rous P [1]               |
| 1951          | Murine leukemia virus                     | Gross L [2]              |
| 1964          | Feline leukemia virus                     | Jarrett et al. [4]      |
| 1964          | Bovine leukemia virus                     | Dutcher et al. [5]      |
| 1970          | Mason-Pfiar monkey virus (MPMV) (First primate retrovirus) | Chopra and Mason [7] |
| 1980          | Human T-cell leukemia virus I (HTLV-I) (First human retrovirus) | Poiesz et al. [12] |
| 1982          | Human T-cell leukemia virus II (HTLV-II) (Second human retrovirus) | Kalyanaraman et al. [13] |
| 1983          | Lymphadenopathy-associated virus (LAV) (Third human retrovirus) | Barre-Sinoussi et al. [15] |
| 1984          | Human T-lymphotropic retrovirus III (HTLV-III) (Third human retrovirus) | Gallo et al. [16,17] |

*For details, see [21].

Reverse Transcriptase and Retroviruses

Early studies of avian and murine retroviruses showed that the intracellular state of these RNA viruses was an integrated DNA, called the proviral intermediate. Prior to the discovery of reverse transcriptase (RT), it was difficult to determine how an RNA virus could take the form of a DNA genome, a process known as reverse transcription because it reverses the standard direction (DNA to RNA) of the flow of genetic information. The discovery, however, of RNA-dependent DNA polymerase in virions of retroviruses by Temin and Mizutani [9] and by Baltimore [10] in 1970 provided a mechanism to support the existence of a proviral intermediate during the growth of retroviruses. This enzyme, RT, transcribes the viral RNA into DNA, which can then integrate into host DNA. Since RT is uniquely associated with the replication of retroviruses, it provides a sensitive biochemical assay system for the detection of this group of viruses.

Discovery of T-Cell Growth Factors and Isolation of Human Retroviruses

Numerous attempts to isolate human retrovirus from human leukemic cells were hindered in part by difficulties encountered in growing human leukemic cells in cultures. The discovery of T-cell growth factor (TCGF), now called interleukin-2 (IL-2), which allows for the productive growth of T cells in cultures [11], was crucial to the subsequent isolation of human retroviruses. The first human retrovirus, the human T-cell lymphotropic virus (HTLV-I), was isolated from cultured leukemic cells obtained from a patient with cutaneous T-cell lymphoma [12]. The second human retrovirus, also a human T-cell lymphotropic virus (HTLV-II), was similarly isolated from leukocyte cultures derived from a patient with hairy-cell leukemia [13]. With these discoveries, an era of human retrovirus research had begun.
Retroviridae\cite{24,25}.

the
can
generation
exogenous
virus
Morphology
shows
individuals
of
group),
replicate
AIDS
clonal
development
quantities
of
human
retroviruses
(Table 2),
probes
for
lymphotropic
virus
III
(HTLV-III)
\cite{16,17},
and
the
AIDS-related
group
of
viruses
(ARV)
\cite{18,19}.
A
combination
of
techniques
originally
developed
for
the
avian
and
murine
retroviruses,
together
with
the
successful
growth
of
human
leukemia
cells
in
culture,
allowed
for
the
isolation
and
identification
of
this
group
of
human
retroviruses.
Indeed,
HIV
was
grown
in
human
T-lymphocytes
stimulated
by
the
growth
factor
IL-2,
and
its
presence
was
identified
by
the
RT
assay
method.
Unlike
most
of
the
mammalian
retroviruses,
the
RT
assay
for
HIV
prefers
Mg$^{++}$
over
Mn$^{++}$
for
its
catalytic
activities
\cite{20}.

Montagnier
and
colleagues
first
reported
in
1983
on
the
isolation
of
an
AIDS
virus.
Because
the
isolate
had
been
obtained
from
a
patient
with
lymphadenopathy
syndrome,
the
virus
was
originally
named
lymphadenopathy-associated
virus
(LAV)
\cite{15}.
Simultaneously,
Gallo
and
colleagues
concentrated
their
efforts
on
establishing
cell
lines
for
propagating
retrovirus
and
identification
of
isolates
obtained
from
AIDS
patients
\cite{16,17}.
Isolates
obtained
by
the
latter
studies
were
reported
as
human
T-cell
lymphotropic
virus
III
(HTLV-III).
The
establishment
of
a
cell
line,
H9,
from
a
leukemia
patient
facilitated
the
propagation
of
the
virus
and
the
production
of
large
quantities
of
human
retroviruses
\cite{16}.
Large-scale
production
of
HIV
permitted
the
development
of
serologic
tests
for
screening
blood
samples,
the
production
of
monoclonal
antibody
for
epidemiological
surveys,
and
the
preparation
of
cloned
DNA
probes
for
studying
the
molecular
mechanisms
of
the
human
retrovirus
infection.
The
chronological
history
of
the
discovery
of
human
retroviruses
and
the
demonstration
of
AIDS
as
a
retroviral
disease
has
been
detailed
in
a
recent
report
\cite{21}.

RETROVIRUS CLASSIFICATION AND PROPERTIES

Classification of Retroviruses

The
family
of
Retroviridae
consists
of
RNA
viruses
that
infect
man
and
animals
and
replicate
through
a
DNA
intermediate—the
proviral
DNA.
The
virion
has
a
diameter
of
100
nm
with
a
lipid
bilayer
envelope
which
surrounds
an
icosahedral
core
containing
a
helical
nucleocapsid
(Fig. 1). The
retrovirus
family
comprises
three
subfamilies
(Table 2),
the
Oncovirinae
(RNA
tumor
virus
group),
the
Spumavirinae
(foamy
virus
group),
and
the
Lentivirinae
(slow
virus
group).
Within
the
lentivirus
subgroup,
HIV
shows
a
closer
relationship
with
equine
infectious
anemia
virus
(EIAV)
than
with
visna
virus
or
caprine
arthritis
encephalitis
virus
(CAEV)
\cite{22}.

Retroviruses
can
exist
endogenously;
that
is,
the
virus
is
transmitted
vertically
from
generation
to
generation.
For
example,
the
guinea
pig
retrovirus,
being
endogenous,
can
be
activated
in
cultured
cells
by
chemical
induction
\cite{8,23}.
On
the
other
hand,
an
exogenous
retrovirus,
for
example
HIV,
is
transmitted
horizontally
from
infected
individuals
to
uninfected
susceptible
hosts.

Morphology of HIV

Members
of
the
HIV
group
are
morphologically
similar
to
other
members
of
the
Retroviridae\cite{24,25}.
As
with
other
retroviruses,
HIV
particles
are
formed
by
budding
through
cytoplasmic
membranes
(Fig. 2A–2C).
During
in vitro
cultivation
of
HIV
in
the
H9
cell
line,
budding
virus
particles
are
observed
three
tofour
days
post-infection,
**FIG. 1.** Schematic diagram of a human immunodeficiency virus (HIV).

**TABLE 2**  
The Retroviridae Family and Representative Virus Strains

| Subfamily          | Virus Strain                                              | Vertebrate Host |
|--------------------|-----------------------------------------------------------|-----------------|
| **Oncovirinae**    |                                                           |                 |
| Group B            | Mouse mammary tumor virus (MMTV)                          | Mice            |
| Group C            | Avian sarcoma virus (ASV)                                 | Chicken         |
|                    | Murine leukemia virus                                     | Mice            |
|                    | Feline leukemia virus                                     | Cats            |
|                    | Bovine leukemia virus                                     | Cattle          |
|                    | Human T-cell leukemia virus-I                             | Human           |
|                    | Human T-cell leukemia virus-II                            | Human           |
| Group D            | Mason-Pfizer monkey virus                                 | Monkey          |
| Ungrouped          | Guinea pig leukemia virus                                 | Guinea pigs     |
| **Spumavirinae**   |                                                           |                 |
|                    | Simian foamy virus                                        | Monkey          |
|                    | Human foamy virus                                         | Human           |
|                    | Feline syncytial virus                                    | Cats            |
|                    | Bovine syncytial virus                                    | Cattle          |
| **Lentivirinae**   |                                                           |                 |
|                    | Visna/maedi virus                                         | Sheep           |
|                    | Equine infectious anemia virus                             | Horse           |
|                    | Caprine arthritis encephalitis virus                      | Goat            |
|                    | Human immunodeficiency virus-1 (HIV-1)                    | Human           |
|                    | Lymphadenopathy-associated virus (LAV-1)                  | Human           |
|                    | Human T-lymphotropic retrovirus III (HTLV-III)            | Human           |
|                    | AIDS-associated retrovirus (ARV)                          | Human           |
|                    | Human immunodeficiency virus-2 (HIV-2)                    | Human           |
|                    | Lymphadenopathy-associated virus (LAV-2)                  | Human           |
|                    | Simian T-cell lymphotropic virus-III (STLV-III)           | Monkey          |
|                    | Human T-cell lymphotropic virus IV                         | Human           |

*Morphologically, "A" type virus particles are commonly found intracellularly and are considered to be immature virus particles.

*See [8,23].
at which time RT is first detected. Intracellular virus particles are not found, although extracellular mature virus particles, 100 nm in diameter, are scattered around the infected cell and are easily identified after seven to ten days of in vitro cultivation (Fig. 2D). The virus particles contain either a central or an eccentric dense core with or without a characteristic bar-shaped band (Fig. 3A). Spikes on the enveloped viral surfaces are not easily identified [20,24]. We have, however, recently found that these surface projections were clearly seen (Fig. 3B) when the infected cells were post-fixed in osmium tetroxide solution containing potassium ferrocyanide, a mixture previously used for preservation of membranes, especially glycogen membranes [26]. Similar but
less distinct projections were visible on virus particles in thin sections of HIV-infected cells treated with tannic acid prior to embedding [25].

Viral Genome and Viral Protein of HIV

The genomic organization of HIV, like other retroviruses, includes long terminal repeats (LTR) at both the 5' and 3' ends, the group-specific gene (gag), the polymerase gene (pol), and the envelope gene (env). In addition, HIV contains four other genes: the transactivating element (tat), the translational controller (trs/art), the short open reading frame (sor), and another open reading frame (orf). These last four genes encode proteins that help to control the expression of HIV [27]. A schematic diagram of the HIV genome and protein products is illustrated in Fig. 4. The major core

FIG. 3. Mature virus particles seen extracellularly at higher magnification. Bar represents 0.2 μ. A. Sample was fixed in 1 percent OSO₄; virus particles with bar-shaped bands (BN), eccentric (E), and central (C), dense cores. B. Sample was fixed in 1 percent OSO₄ containing 2.5 percent potassium ferrocyanide; club-shaped projections were seen surrounding each virus particle.
proteins are p24 and p18. The bilayer envelope is studded with glycoproteins. The major glycoproteins of the envelope gene are gp41 and gp120 (see Figs. 1 and 4). Sera from AIDS patients with advanced disease sometimes show greatly diminished intensity to the p24 protein band when compared with sera from pre-AIDS patients [28,29]. Therefore, the measurement of antibody to p24 protein has been used as a convenient indicator regarding the stage of the disease in AIDS patients.

LABORATORY DIAGNOSIS OF HIV INFECTION

Serologic Tests for HIV Antibody

Since 1984 there has been a steady and rapid increase in knowledge about the pathogenesis of HIV infection. Early studies showed that antibodies to HIV were present in close to 90 percent of AIDS patients and in more than 75 percent of patients with pre-AIDS syndromes [30]. Since May 1985, commercially licensed enzyme-linked immunosorbent assay (ELISA) kits have been used for testing blood or plasma from normal blood donors for HIV antibody [30–33]. These tests are now accepted as having good sensitivity and specificity for screening blood donors. Their use has resulted in the almost complete elimination of HIV-contaminated blood or blood products from the nation's blood supply and have rendered transfusion much safer.

Because the ELISA test was originally developed for screening the blood of donors, however, these tests are very sensitive, and false-positive reactions have been noted [32]. Therefore, all sera reacting positively by ELISA tests must be confirmed by other, more specific techniques; e.g., the Western blot immunoassay [34,35] or by immunofluorescence [36]. Some false positives have been found to be due to human leukocyte antigen (HLA) present in HIV reagent prepared from H9 cells [37–42]. As is the case with other viral infections, isolation and identification of the infectious agent permit a definitive and specific diagnosis.
HIV Isolation and Identification

Although serodiagnosis is now widely used for detecting HIV infection, none of the tests currently available are able to differentiate perfectly infected from non-infected individuals. Isolation of HIV from clinical specimens, though tedious and time-consuming, offers the advantage of confirmation that the person is actually infected with HIV. General principles and detailed procedures for the isolation and identification of HIV are included in the paper by Griffith in this issue [43], and many more techniques are expected to be developed in the years to come. As easier and more rapid methods become available for the isolation and cultivation of this virus, the virology laboratory service will play a larger role in the management of HIV-infected individuals.

Significance of Laboratory Diagnosis

HIV has been isolated from blood [15–19] and other body fluids of infected patients including semen, vaginal secretions, tears, saliva, breast milk, and cerebrospinal fluid [44–51]. Transmission of HIV by sexual contact with infected individuals, by receiving contaminated blood or blood products, or by perinatal exposure of children born to infected mothers is well documented [52–55]. Many individuals may be infected with the virus for years without showing any signs or symptoms and yet can transmit the virus to others by blood donation or by sexual contact. Thus, laboratory testing for HIV infection should be helpful, especially with the high-risk groups, in preventing further transmission of this viral disease.

ACKNOWLEDGEMENTS

This study was partially supported by the Medical Research Funds from the Veterans Administration and by Research Contract AI 62519 from the National Institute of Allergy and Infectious Diseases. The H9 cell and HIV (HTLV-III B) originally isolated by Dr. Robert Gallo and associates at the National Cancer Institute were obtained through the courtesy of Dr. Martin Hirsch of Massachusetts General Hospital, Harvard Medical School. The excellent assistance of Sigrid Klein for electron microscopy and Helen Losnes for manuscript preparation is greatly appreciated.

REFERENCES

1. Rous P: A sarcoma of the fowl transmissible by an agent separable from the tumor cells. J Exp Med 13:397–411, 1911
2. Gross L: “Spontaneous” leukemia developing in C3H mice following inoculation in infancy, with AK-leukemic extracts, or AK-embryos. Proc Soc Exp Biol Med 76:27–32, 1951
3. Gross L: Oncogenic Viruses, 3rd edition. Volume 1, Mouse Leukemia. Oxford, New York, Pergamon Press, 1983, pp 305–443
4. Jarrett WFH, Crawford EM, Martin WB, Davie F: Leukemia in the cat. A virus-like particle associated with leukemia (lymphosarcoma). Nature 202:567–569, 1964
5. Dutcher RM, Larkin EP, Marshap RR: Virus-like particles in cow’s milk from a herd with a high incidence of lymphosarcoma. JNCI 33:1055–1064, 1964
6. Klein G (ed): Viral Oncology: RNA tumor viruses. New York, Raven Press, 1980, pp 1–431
7. Chopra HC, Mason MM: A new virus in a spontaneous mammary tumor of a rhesus monkey. Cancer Res 30:2081–2086, 1970
8. Hsiung GD, Fong CKY, Evans CH: Prevalence of endogenous oncornavirus in guinea pigs. Intervirology 3:319–331, 1974
9. Temin HM, Mizutani S: RNA-dependent DNA polymerase in virions of Rous sarcoma virus. Nature 226:1211–1213, 1970
10. Baltimore D: RNA-dependent DNA polymerase in virions of RNA tumor viruses. Nature 226:1209–1211, 1970
11. Poiesz BJ, Ruscetti FW, Mier JW, Woods AM, Gallo RC: T-cell lines established from human T-lymphocytic neoplasias by direct response to T-cell growth factor. Proc Natl Acad Sci USA 77:6815–6819, 1980

12. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC: Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. Proc Natl Acad Sci USA 77:7415–7419, 1980

13. Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M, Miyoshi I, Blayney D, Golde D, Gallo RC: A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia. Science 218:571–573, 1982

14. Human Retrovirus Subcommittee: Human immunodeficiency viruses (Letter). Science 232:697, 1986

15. Barre-Sinoussi F, Chermann JC, Rey F, Nugeyre MY, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vezinet-Brun F, Rouzioux C, Rozenbaum W, Montagnier L: Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 220:868–871, 1983

16. Popovic M, Sarngadharan MG, Read E, Gallo RC: Detection, isolation and continuous production of cytopathic retroviruses (HTLV-III) from patients with AIDS and pre-AIDS. Science 224:497–500, 1984

17. Gallo RC, Salahuddin SZ, Popovic M, Shearer GM, Kaplan M, Haynes BF, Palker TJ, Redfield R, Oleske J, Safai B, White G, Foster P, Markham PD: Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 224:500–503, 1984

18. Feorino PM, Kalyanaraman VS, Haverkos HW, Cabradilla CD, Warfield DT, Jaffe HW, Harrison AK, Gottlieb MS, Goldfinger D, Chermann JC, Barre-Sinoussi F, Spira TT, McDougal JS, Curran JW, Montagnier L, Murphy FA, Francis DP: Lymphadenopathy associated virus infection of a blood donor recipient pair with acquired immunodeficiency syndrome. Science 225:69–72, 1984

19. Levy JA, Hoffman AD, Kramer SM, Landis JA, Shimabukuro JM, Oshiro LS: Isolation of lymphotropic retroviruses from San Francisco patients with AIDS. Science 225:840–842, 1984

20. Salahuddin SZ, Markham PD, Wong-Staal F, Gallo RC: The human T-cell leukemia-lymphoma virus family. Prog Med Virol 32:195–211, 1985

21. The chronology of AIDS research (Commentary). Nature 326:435–436, 1987

22. Goudsmitt J, Houwers DJ, Smit L, Nauta IM: LAV/HTLV-III gag gene product p24 shares antigenic determinants with equine infectious anemia virus but not with visna virus or caprine arthritis encephalitis virus. Intervirology 26:169–173, 1986

23. Dahlberg JE, Tronick SR, Aaronson SA: Immunological relationships of an endogenous guinea pig retrovirus with prototype mammalian type B and type D retroviruses. J Virology 33:522–530, 1980

24. Palmer E, Sporborg C, Harrison A, Martin ML, Feorino P: Morphology and immunoelectron microscopy of AIDS virus. Archives of Virology 85:189–196, 1985

25. Gelderblom HR, Hausmann EHS, Ozel M, Pauli G, Koch MA: Fine structure of human immunodeficiency virus (HIV) and immunolocalization of structural proteins. Virology 156:171–176, 1987

26. Russel L, Burguret S: Ultrastructure of leydig cells as revealed by tissue section treatment with a ferrocyanide osmium mixture. Tissue Cell 9:751–766, 1977

27. Ratner L, Haseltine W, Patarca R, Livak KJ, Stachic B, Josephs SF, Doran ER, Rafalski JA, Whitehorn EA, Baumeister K, Ivanoff L, Petteway SR, Pearlson ML, Lautenberger JA, Papas TSW, Ghrayeb J, Chang NT, Gallo RC, Wong-Staal F: Complete nucleotide sequence of the AIDS virus, HTLV-III. Nature (London) 313:277–284, 1985

28. Schupbach J, Haller O, Vogt M, Lurth R, Joller H, Oelz O, Popovic M, Sarngadharan MG, Gallo RC: Antibodies to HTLV-III in Swiss patients with AIDS and Pre-AIDS and in groups at risk for AIDS. N Engl J Med 312:265–270, 1985

29. Burke DS, Redfield RR, Putman P, Alexander SS: Variations in Western blot banding patterns of human T-cell lymphotropic virus type III/lymphadenopathy-associated virus. J Clin Micro 25:81–84, 1987

30. Sarngadharan MG, Popovic M, Bruch L, Schupbach J, Gallo RC: Antibodies reactive with human T-lymphotropic retrovirus (HTLV-III) in the serum of patients with AIDS. Science 224:506–508, 1984

31. Petricciani JC: Licensed tests for antibody to human T-lymphotropic virus type III. Sensitivity and specificity. Ann Int Med 103:726–729, 1985

32. Waldman AA, Colman M: Serum screening for anti-HTLV-III antibodies II, Screening tests. Laboratory Management 24:31–34, 1986
33. Carlson JR, Bryant ML, Hinrichs SH, Yamamoto JK, Levy NB, Yee J, Higgins J, Levine AM, Holland P, Gardner MB, Pedersen NC: AIDS serology testing in low- and high-risk groups. JAMA 253:3405–3408, 1985
34. Esteban JJ, Tai CC, Kay JWD, Shih JW, Bodner AJ, Alter JH: Importance of Western blot analysis in predicting infectivity of anti-HTLV-III/LAV positive blood. Lancet ii:1083–1086, 1985
35. Waldman AA, Oleszko WR: Serum-screening for anti-HTLV-III antibodies II. Confirmatory tests. Laboratory Management 24:45–51, 1986
36. Sandstrom EG, Schooley RT, Ho DD, Byington R, Sarngadharan MG, MacLane ME, Essex M, Gallo RC, Hirsch MS: Detection of human anti-HTLV-III antibodies by indirect immunofluorescence using fixed cells. Transfusion 25:308–312, 1985
37. Kuhnl P, Seidl S, Holzberger G: HLA DR4 antibodies cause positive HTLV-III antibody ELISA results. Lancet i:1222–1223, 1985
38. Weiss SH, Mann DL, Murray C, Popovic M: HLA-DR antibodies and HTLV-III antibody ELISA test. Lancet i:157, 1985
39. Hunter JB, Menitove JE: HLA antibodies detected by ELISA HTLV-III antibody kits. Lancet ii:397, 1985
40. Sayers MH, Beatty PG, Hansen JA: HLA antibodies as a cause of false-positive reactions in screening enzyme immunoassay for antibodies to human T-lymphotropic virus Type III. Transfusion 26:113–115, 1986
41. Blanton M, Balakrishman K, Dumaswala U, Zelenski K, Greenwalt TJ: HLA antibodies in blood donors with reactive screening tests for antibody to the immunodeficiency virus. Transfusion 27:118–119, 1987
42. Yu SK, Fong CKY, Landry ML, Hsiung GD, Solomon LR: A false positive HIV antibody reaction due to transfusion-induced HLA-DR sensitization. Submitted for publication
43. Griffith BP: Principles of laboratory isolation and identification of the human immunodeficiency virus (HIV). Yale J Biol Med 60:575–587, 1987
44. Zagury D, Bernard J, Leibowitch J, Safai B, Groopman JE, Feldman M, Sarngadharan MG, Gallo RC: HTLV-III in cells cultured from semen of two patients with AIDS. Science 226:449–451, 1984
45. Fujikawa LS, Salahuddin SZ, Palestine AG, Masur H, Nussenblatt RB, Gallo RC: Isolation of human T-lymphotropic virus type III from the tears of a patient with the acquired immunodeficiency syndrome. Lancet ii:529–530, 1985
46. Groopman JE, Salahuddin SZ, Sarngadharan MG, Markham PD, Gonda M, Sliski A, Gallo RC: HTLV-III in saliva of people with AIDS-related complex and healthy homosexual men at risk for AIDS. Science 226:447–449, 1984
47. Thiry L, Sprecher-Goldberger S, Jonckheer T, Levy J, Van de Perre P, Henrivaux P, Cogniaux-LeClere J, Clumeck N: Isolation of AIDS virus from cell-free breast milk of three healthy virus carriers [Letter]. Lancet ii:891–892, 1985
48. Vogt MW, Witt DJ, Craven DE, Byington R, Crawford DF, Schooley RT, Hirsch MS: Isolation of HTLV-III/LAV from cervical secretions of women at risk for AIDS. Lancet i:525–527, 1986
49. Wofsy CB, Cohen JB, Hauer LB, Padian NS, Michaelis BA, Evans LA, Levy JA: Isolation of AIDS-associated retrovirus from genital secretions of women with antibodies to the virus. Lancet i:527–529, 1986
50. Ho DD, Rota TR, Schooley RT, Kaplan JC, Allan JD, Groopman JE, Resnick LR, Felsenstein D, Andrews CA, Hirsch MS: Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. N Engl J Med 313:1493–1497, 1985
51. Levy JA, Shimabukuro J, Hollander H, Mills J, Kaminsky L: Isolation of AIDS-associated retroviruses from cerebrospinal fluid and brain of patients with neurological symptoms. Lancet ii:586–588, 1985
52. Duncan ED, Miller HJ, McKeever WP: Non-Hodgkin lymphoma, HTLV-111/LAV and HTLV-111/LAV antibody in the wife of a man with transfusion-acquired AIDS. Am J Med 81:898–900, 1986
53. Ward JW, Deppe DA, Samson S, Perkins H, Holland P, Fernando L, Feorino PM, Thompson P, Kleinnans S, Allan JR: Risk of human immunodeficiency virus infection from blood donors who later developed the acquired immunodeficiency syndrome. Ann Int Med 106:61–62, 1987
54. Human immunodeficiency virus infection in transfusion recipients and their family members. MMWR 36:137–139, 1987
55. CDC additional recommendations to reduce sexual and drug abuse-related transmission of human T-lymphotropic virus type 111/lymphadenopathy-associated virus. MMWR 35:152–155, 1986