

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20208

Building 37, Room 6A09
(301) 496-6007

April 8, 1985

Harold E. Varmus, M.D.
Chairman, Retrovirus Study Group
Department of Microbiology and
Immunology
School of Medicine
University of California
San Francisco, California 94143

Dear Harold,

Thanks for your letter of March 4th. As you already know I am pleased to be with you on this subcommittee for nomenclature of human retroviruses.

I was not sure about one point in your letter. You mentioned there is no trouble with HTLV-I, II as type-C oncornaviruses. Actually, there really is a bit of a problem there too. That is why many of us at the Japan HTLV meeting in November sought an overall class e.g. type T with the same HTLV-I, II, III, etc. nomenclature. The reason is that HTLV-I and II as well as BLV morphologically and antigenically are different than the type-C (mouse, rat, cat, gibbon, woolly, etc.)

I will summarize why I believe HTLV-III is a fair, accurate, and safe term to use, in short the reasons why I hope it will stay, and that this will not become more of a problem.

1. Common usage: It is already used by the vast majority of scientists, clinicians, and administrators.
2. Precedent of work: This, of course, gets into the first debate. What is precedent and when does it begin. One can logically argue that precedent begins in this case with the virus of AIDS itself and only this virus or the work which began human retrovirology.
3. Precedent in agreement: See the Cold Spring Harbor signed agreement made in November 1983 which advocates HTLV-III.
4. Precedent in previous retrovirology: I think it is useful to keep a species name as in feline..., human..., for several reasons. Therefore, I believe H and V (virus) are unavoidable.

5. Accuracy: The most striking, remarkable, and common feature of all known human retroviruses is their pronounced lymphotropism, especially T-cell and most especially mature T4 helper cell both in vitro and in vivo. When one recognizes how many types of lymphocytes there are and the various subsets of T-cells, this has got to make an impression. In this respect LAV either for lymphadenopathy virus or as Montagnier now wants it as lymphadenopathy AIDS virus (still being LAV) is not exact. Many things cause lymphadenopathy. Moreover, the virus causes more than AIDS. For example, we now know that AIDS is one of many disorders caused by HTLV-III. The virus has now been associated with teratogenic effects, brain disease in the absence of AIDS, several types of lymphomas and several types of carcinomas in the absence of AIDS, and thrombocytopenic purpura to name some.
6. Safety: As you know this is a disease of great emotion, fear, sensationalism, and psychic and social trauma. We did not arrive casually at the name. To push a term AIDS virus or AIDS related virus in my opinion is a huge mistake with potential damage. It is an opinion brought to my attention by several clinicians. I seriously doubt whether blood banks or many clinical people will ever use that term.
7. Consistency: We have kept to one terminology from the start. LAV was previously IDAV and before that a Human T-Lymphotropic Virus.
8. Scientific accuracy: I have heard a great deal of how this is not close to HTLV-I and II, therefore it should not be III etc. There is no doubt, this virus is not close in homology to I or II. One can list numerous differences. That is all obvious from the sequence data and even from earlier reports it could be surmised. We have published distant homology to visna, yet visna and the lenti-retroviruses not only are not T4 tropic, apparently they are not even lymphotropic. Also, at this stage one should note that Montagnier et al. have twice reported no homology to visna.

There are, however, several important features in common with HTLV-I and II in biology, immunology, molecular biology, and clinical disease. Some are shared with a few other retroviruses, while others appear to be unique at this stage. I have listed these below to the best of my ability even including the self-evident ones and even ones which may not have a bearing in nomenclature for the sake of thought.

- 1) HTLV-III like I and II is a human, exogenous retrovirus.
- 2) It is lymphotropic infecting some B and many T-cells just like HTLV-I and II.
- 3) It is particularly T4 tropic like I and II.
- 4) In vitro HTLV-III induces formation of T-cell syncytia with enormous multinucleated cells. So do HTLV-I and II.

- 5) In vitro HTLV-I and II can impair T-cell immune function. Obviously III does it better and doesn't immortalize while I and II immortalize some T-cells.
- 6) Disease by HTLV-III is chiefly of T4 cells - same for HTLV-I and II.
- 7) HTLV-I apparently causes opportunistic infections and moderate immunosuppression in vivo e.g., clinicians describe Pneumocystis Carinii with HTLV-I (see also Essex's studies of infectious disease wards in Japan).
- 8) Origin - HTLV-I almost surely originated from Africa. Same for HTLV-III.
- 9) Presence in more than one species: HTLV-I has been found in Old World monkeys. This was unique among all known retroviruses (i.e. in more than one species). The same has been recently discovered by Essex and co-workers with HTLV-III.
- 10) Manner of Transmission: HTLV-I is transmitted by sex (the data suggest by semen) and by blood transfusions and by intravenous drug addiction (like HTLV-III).
- 11) Common p24 antigenic determinant: We find that HTLV-I, II, and III share a common antigenic determinant not shared by other retroviruses. We do confirm a weak cross way with equine infectious anemia virus reported by Montagnier and co-workers. Our data of the p24 relatedness of HTLV-I, II, and III was with both a rabbit heterologous antisera and a human monoclonal antibody. Reactivities with the latter have not been found with other retroviruses.
- 12) There is nucleotide sequence homology in pol of HTLV-III to gag-pol sequences of I and II as well as some in the LTR. Also the first short open reading frame (we call it SOR) which follows the pol gene appears to be a vestigial env gene. It has homology with HTLV-I env.
- 13) There is a double splice to create a novel 3' mRNA. To my knowledge this is unique to HTLV-I, II and III.
- 14) There is an extra gene at the 3' end.
- 15) The 3' mRNA is about 2 Kb in all.
- 16) The LTRs activity promote the CAT gene expression (trans-acting transcriptional activation) when cells are infected with the corresponding virus. Although this may not be unique to these viruses, it appears to be uncommon in others and not as marked (100 to 2000 X SV40 from Haseltine data).

- 17) The p24 is juxtaposed to the NH₂-terminal gag gene product, i.e., no phosphoprotein in this position. I believe this is unique to HTLV-I, II, III and BLV.
- 18) The relatively small size of the major core protein (p24), although, of course, not unique is consistent with I and II.
- 19) The Mg⁺⁺ requirement of the RT is again not unique but consistent with I and II.
- 20) Arsene Burny has a monoclonal to env of BLV. I think this crosses with env of HTLV-I and HTLV-III.

9. Derivation of all the AIDS virology work: In February 1982 when I (with discussions with H. Essex) first formally proposed AIDS was caused by a human T-lymphotropic retrovirus at an AIDS Cold Spring Harbor meeting, there was not one single grant approved in the U.S. to study this possibility. It seems every other virus but the right type were studied. We formed an NIH-NCI Task Force designed to find the cause of AIDS in the Summer of 1982. As the 20-25 or so members can tell you all the AIDS work was highly derivative of the HTLV-I and II work first in its conception, second, in the technology to grow the right cells (same protocol for isolation as for I and II), and lastly in the approach used to link it to disease and characterize it.

Finally, it is important to emphasize that the term HTLV-III never depended on extensive or even any significant homology to HTLV-I and II (refer again to Cold Spring Harbor meeting). In fact, when I named HTLV-II we had evidence of no homology to HTLV-I. It was only later with very relaxed conditions of hybridization and eventually sequence data which proved some homology.

For the above reasons I hope the committee will agree that this currently used term makes sense.

Sincerely yours,



Robert C. Gallo, M.D.
Chief, Laboratory of Tumor
Cell Biology

RCG/am

cc:	:
J. Coffin	A. Haese
M. Essex	J. Levy
S. Oroszlan	L. Montagnier
N. Teich	H. Temin
K. Toyoshima	P. Voot
H. Varmus	R. Weiss