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# NATURAL HISTORY OF HTLV III INFECTION IN USAF PERSONNEL: CLINICAL EVALUATION, LABORATORY EVALUATION, ASSESSMENT OF IN VIVO AND IN VITRO IMMUNOLOGIC STATUS, AND DATA STORAGE

AD-A224 345

ANNUAL REPORT

BY

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December 1988

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-86MM6508

WILFORD HALL USAF MEDICAL CENTER
LACKLAND AFB, TX 78236-5300

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SECURITY CLASSIFICATION OF THIS PAGE

# REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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|---|---|
| 1a. REPORT SECURITY CLASSIFICATION<br>Unclassified | 1b. RESTRICTIVE MARKINGS |
| 2a. SECURITY CLASSIFICATION AUTHORITY | 3. DISTRIBUTION/AVAILABILITY OF REPORT<br>Approved for public release; distribution unlimited |
| 2b. DECLASSIFICATION/DOWNGRADING SCHEDULE | |
| 4. PERFORMING ORGANIZATION REPORT NUMBER(S) | 5. MONITORING ORGANIZATION REPORT NUMBER(S) |
| 6a. NAME OF PERFORMING ORGANIZATION<br>Wilford Hall USAF Medical Center<br>6b. OFFICE SYMBOL (If applicable)<br>SGHMM | 7a. NAME OF MONITORING ORGANIZATION |
| 6c. ADDRESS (City, State, and ZIP Code)<br>Lackland AFB, TX 78236-5300 | 7b. ADDRESS (City, State, and ZIP Code) |
| 8a. NAME OF FUNDING/SPONSORING ORGANIZATION<br>Research Development Command<br>8b. OFFICE SYMBOL (If applicable) | 9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER<br>DAMD17-86MM6508 |
| 8c. ADDRESS (City, State, and ZIP Code)<br>Fort Detrick<br>Frederick, Maryland 21701-5012 | 10. SOURCE OF FUNDING NUMBERS<br>PROGRAM ELEMENT NO. 63105A<br>PROJECT NO. 3M2-63105DH29<br>TASK NO. AA<br>WORK UNIT ACCESSION NO. 024 |

11. TITLE (Include Security Classification)
Natural History of HTLV III Infection in USAF Personnel: Clinical Evaluation, Laboratory Evaluation, Assessment of In Vivo and In Vitro Immunologic Status, and Data Storage

12. PERSONAL AUTHOR(S)

| 13a. TYPE OF REPORT | 13b. TIME COVERED | 14. DATE OF REPORT (Year, Month, Day) | 15. PAGE COUNT |
|---|---|---|---|
| Annual | FROM 87/9/15 TO 88/9/14 | 1988 December | |

16. SUPPLEMENTARY NOTATION

| 17. COSATI CODES | | | 18. SUBJECT TERMS (~~Continue on reverse if necessary and identify by block number~~) |
|---|---|---|---|
| FIELD | GROUP | SUB-GROUP | HTLV III/HIV natural history, HIV disease progression, USAF active duty military HIV, HIV neurological disease, RAI, prognostic markers of disease progression, sensory-neural |
| 06 | 03 | | |
| 06 | 13 | | |

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The Wilford Hall USAF Medical Center HIV Scientific Study Group has continued our investigation into the Natural History of HIV disease in active duty USAF personnel and their dependants with intensive immunological evaluation and staging according to the Walter Reed staging classification. Significant progression over 12 months of observation appears to be approximately 10%. Studies to determine a marker of disease progression other than absolute CD4a lymphocyte counts are ongoing.

Our large neurological natural history study has continued on all active duty HIV-seropositive individuals and they continue to receive full neurological evaluations as well as CSF analysis. Our data demonstrate that the CSF immune response is maximal in early-stage HIV disease and more blunted with respect to both absolute CSF lymphocyte numbers and B-cell immunologic response when CD4a counts drop below 400 cells/$mm^3$. Ongoing evaluation of

| 20. DISTRIBUTION/AVAILABILITY OF ABSTRACT | 21. ABSTRACT SECURITY CLASSIFICATION |
|---|---|
| ☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS | Unclassified |
| 22a. NAME OF RESPONSIBLE INDIVIDUAL<br>Mary F. Bostian | 22b. TELEPHONE (Include Area Code)<br>(301) 663-7325<br>22c. OFFICE SYMBOL<br>SGRD-RMI-S |

DD Form 1473, JUN 86 *Previous editions are obsolete.* SECURITY CLASSIFICATION OF THIS PAGE

Continued from #18

hearing loss, immunologic function, T-lymphocyte function

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cognitive function of HIV-infected individuals demonstrates that health-related anxiety may adversely affect neuropsychological testing when accomplished in association with an individual being first told that they were HIV seropositive. Further, differences in cognitive function, however subtle, were noted in individuals with CD4a counts less than 220/$mm^3$ compared to those with normal CD4a counts, and finally that clinical AIDS dementia complex affects less than 10% of the USAF HIV-infected population in late-stage disease. CSF anti-cardiolipin IgG levels may serve as a potential marker for development of HIV-related CNS disease. Studies involving nerve conduction demonstrate a progressive decline in nerve conduction parameters associated with the decline in CD4a counts in HIV-infected individuals. An extensive evaluation of oral hairy leukoplakia demonstrates that OHL is a significant marker for disease progression but the percentages of progression to AIDS from early stage disease may be much lower than that previously reported which may reflect the overall earlier stage disease of our patient population.

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## I. Natural History

During the past year, we have continued our investigation into the natural history of HIV disease in active duty USAF personnel and their dependants. To date, approximately 870 HIV positive patients have been entered into the WHMC databank. Of these approximately 815 have been active duty USAF members, the remainder are dependants and retirees. Approximately 100 patients have met the CDC criteria for the diagnosis of AIDS. Approximately 400 USAF patients have undergone re-evaluation, of these 38% have progressed by the Walter Reed staging criteria, but when discounting progression of Walter Reed stage 1 to stage 2 (28%), 10% of these patients have shown significant progression at 1 year re-evaluation. Of note the rate of progression is much higher in patients who are Walter Reed stage 4 and 5 than in earlier Walter Reed stages. Among variables studied for correlation with disease progression have been absolute CD4a helper lymphocyte count, CD4a to CD8 ratio, serum IgG, IgA, IgM, and IgE, the presence of partial or complete anergy, presence of oral hairy leukoplakia, as well as standard chemistry profiles and hemograms.

## II. T-Lymphocyte Function

In addition, a burgeoning collaboration with investigators at the National Institutes of Health has included work in the lab of Dr Gene Shearer, Dr Jay Berzowsky, and Dr Hana Golding. Investigations in these labs have included: analysis of T-helper cell responses to both mitogens and specific soluble antigens, analysis of responsiveness of T lymphocyte IL-2 production and in vitro proliferation in response to synthetic HIV peptides using peptides generated by Dr Berzowsky, analysis of antibody which cross-reacts with HLA-DR and HIV-1gp41 which may lead to T-lymphocyte depletion and functional impairment of T-lymphocyte responses.

## III. HIV Neurological Disease

In addition, a large neurological natural history study has been conducted whereby all active duty HIV positive individuals receive a neurological evaluation by board certified neurologists. In addition, formal audiometric testing is conducted on all active duty and retired Air Force personnel to assess the impact of HIV on auditory function. Preliminary results reported by Dr Ann Bell indicate that there is a significant hearing impairment in HIV positive individuals beyond that which can be attributed to occupational exposure.

The neurological nitro history study has continued on all active duty HIV seropositive individuals. They continue to receive a complete neurological evaluation by a board certified neurologist and a lumbar puncture to analyze CSF parameters including protein, glucose, nucleated cell count, CSF IgG, IgG index, IgG synthesis rate, oligloconal bands, and in selected cases myelin basic protein, HIV culture and p-24 antigen detection. Selective patients receive detailed neuropsychiatric evaluations, including psychiatric consultation and neuropsychological testing.

Findings thus far in the neurological arm of the study include our observation that the incidence of opportunistic infection, progressive multifocal leukoencephalopathy, and primary CNS lymphoma is parallel to the experience reported nationally. In our study of CSF in 323 neurologically asymptomatic HIV-1 infected USAF personnel with at least 2 CSF studies, and a

minimum of 270 days between analyses, it was found that there are significant ($p<.05$) increases over time in nucleated cell counts, measures of intrathecal IgG production (especially in immunocompetent patients) and decreased protein levels. When CD4a counts drop below 400 cells/$mm^3$, cellular responses and immunologically changes were less impressive. Although weighted towards patients with higher CD4a counts, these data suggest that the CSF immune response is maximal when the patient is immunocompetent and more blunted with respect to both absolute CSF lymphocyte numbers and B-cell immunological response when CD4a counts drop below 400 cells/$mm^3$.

Evaluation of cognitive function of HIV-infected individuals showed important findings in three parallel studies. First, a follow-up study of the patients published in Archives of Neurology, Feb 1989, revealed that in 50 patients who underwent our battery of neuropsychological testing after approximately 1 year revealed that not only was there no significant decline in neuropsychological functioning, but in many of the subtests there were significant improvements. These data were interpreted as indicating that health-related anxiety may adversely impact on neuropsychological testing when accomplished in association with an individual being first told that they are HIV seropositive. Another study reviewed the neuropsychological parameters with respect to both CD4a counts and CSF production of IgG. Consistent with our previous findings, the analysis indicates that patients with abnormal immune parameters (CD4a counts less than 200/$mm^3$, elevated CSF IgG index, or elevated IgG synthesis) had significantly lower scores (but within normal range) on tests measuring motor speed, verbal memory acquisition and visual motor speed, and mental tracking. These data emphasize the need for distinguishing between immunological differences of patients in early and late stages of HIV infection during research assessing cognitive functioning, since subtle cognitive of changes were noted in patients with CD4a counts less than 220/$mm^3$. Finally, the incidence of AIDS dementia complex (ADC) in the USAF population was assesed. Clinical ADC affects less than 10% of the USAF AIDS (WR-6) population, significantly less than the 40-70% predicted by others. Possible explanations for this difference may include: 1) USAF study is population based and not referral biased, 2) Cognitive testing was not always accomplished during the terminal stages of the illness, 3) the average age of our population is less than 30, and/or 4) other centers reflect experience with a more neurotropic virus. All of the above data concerning cognitive function in HIV infected individuals was presented at the American Academy of Neurology in April 1988, and published in Neurology 1989; vol 39 (3) - supplement 1.

In addition, two other neurologically related studies have been accomplished. The first concerned the presence of anti-cardiolipin IgG antibodies in the CSF of HIV infected patients. Twelve patients with high serum anti-cardiolipin IgG/IgM and increased total CSF IgG levels were assayed for CSF anti-cardiolipin antibody IgG/IgM. There was no significant difference between patients and controls for CSF anti-cardiolipin antibody IgM, but 9 of 12 had abnormal CSF anti-cardiolipin IgG levels. CSF anti-cardiolipin IgG levels should, therefore, be evaluated for potential as a marker for development of HIV-related CNS disease. And finally, a study of nerve conduction velocities on nearly 300 HIV-infected individuals, predominantly with no symptoms of peripheral neuropathy, demonstrated a significant difference in groups according to CD4a counts. Clearly those with fewer than 200 CD4a cells/$mm^3$ had several nerve conduction parameters which were significantly different compared to the higher CD4a cell count groups. For several parameters there was a progressive decline in the nerve conduction parameters associated with decline in CD4a counts. These individuals, however,

rarely had any symptoms of peripheral neuropathy. Thus, immunological decline may have associated asymptomatic changes in peripheral nerve which necessitate further study.

IV. Oral Hairy Leukoplakia Study

An investigation into the significance of oral hairy leukoplakia (OHL) has been undertaken and to date approximately 85 cases have been identified across all Walter Reed stages. Of these 72 are confirmed by biopsy. The prevalence of biopsy confirmed OHL in our entire cohort is approximately 9%. When statistical analyses were performed on a battery of laboratory and immunological parameters of OHL-positive vs OHL-negative HIV positive individuals, there were no statistically significant differences seen in the mean values between these two groups. However, a subgroup of seven individuals who have progressed to AIDS from lower Walter Reed stage disease have been observed over a period of 18 months. In this subgroup of individuals, there were statistically significant higher mean serum IgA levels, lower helper/ suppressor ratios and presence of partial or complete anergy (with greater than 400 CD4a positive cells) and a more rapid fall in CD4a cell number over time. Although numbers are small it appears that this patient population partially confirms the results of Greenspan et al, (JID 1987:155;475) who report up to 80% progression to AIDS over a 30 month period. It is felt that our data showed that OHL is a significant marker for disease progression but that percentages of progression to AIDS from early stage disease may be much lower than that reported by Greenspan, et al, because of the overall earlier stage of our patient population.

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5. Parker W, Hensley R. Heterogeneity of the T4 Epitope (T4). Presented at the 1st Annual Flow Cytometry Forum, San Antonio, TX, March 1988

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