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CHARACTERIZATION OF AFRICAN HUMAN RETROVIRUSES RELATED TO HTLV-III/LAV

ANNUAL REPORT

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Various epidemiologic patterns of HIV-2 and HIV-1 suggest both different population dynamics but also different origins. In HIV-2 prevalent areas, the virus demonstrates features of long-term endemicity. Incidence rates for HIV-2 are low as compared to that of HIV-1 and may reflect other in vitro characteristics;decreased infectivity and cytopathicity. Clinico-prospective studies have still failed to demonstrate AIDS or related symptoms in HIV-2 positive individuals followed both clinically and immunologically.

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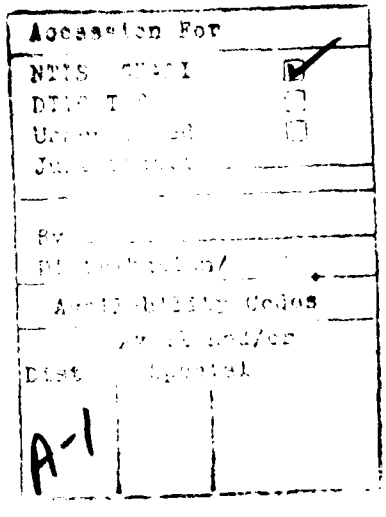
FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 86-23, Revised 1985).

For the protection of human subjects the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.



The primary focus of this grant is to better understand the biology of the West African Human Immunodeficiency VIrus (HIV-2). In the past year, a great deal of progress has been made in a number of areas that help distinguish this virus from the prototype human AIDS virus, HIV-1. As stated in our original specific aims, it is hoped that the results of such comparative studies between HIV-1 and HIV-2 will yield information useful to an effective AIDS vaccine.

EPIDEMIOLOGY

The epidemiologic studies of HIV-2 have continued to demonstrate an unusual geographic distribution for this virus infection in people. Our previous studies had demonstrated high rates of infection in many countries of West Africa with an increasing age-specific prevalence indicative of long-term endemicity of the virus. These studies have been now corroborated by a number of other labs. yet the relatively distinct foci of either HIV-1 and HIV-2 infected regions in sub-Saharan Africa remains a mystery. Most seroepidemiologic studies have been based on sentinel groups in urban areas. There is still a need to study rural areas of HIV-2 endemic countries with a population-based survey. Our prospective studies of female prostitute groups has allowed for determination of HIV-2 incidence which appears quite low (<2%/year), again suggestive of HIV-2 endemicity.

Significant rates of HIV-2 have now been demonstrated in 2 non-West African countries, Angola and Mozambique. Both of these countries border HIV-1 endemic countries such as Zaire and Zambia and an influx of HIV-1 is also seen. Of interest, is that these former Portugese colonies have had long term

relationships with other West African Portugese colonies which also demonstrate high rates of HIV-2 (e.g. Guinea Bissau, Cape Verde).

The patterns of HIV-2 and HIV-1 epidemiology are outlined below and help to distinguish the spread and potential origin of HIV-2 from that of HIV-1. These patterns are based on cross-sectional seroprevalence data in urban centers and therefore most likely represent an exaggeration of the extent of virus infection in a given country. Nonetheless they are illustrative of perhaps sequential stages of HIV-2 infection at a population level and its interaction with spreading HIV-1 given the poorly understood movements of people between various African countries. One hypothetical scenario is that a given population will evolve in time from pattern D to pattern A followed by pattern B. Pattern C may be a result of HIV-1 spread into a pattern B population or conversely the spread of HIV-2 into an HIV-1 endemic population. In both Ivory Coast and Burkina Fasc the increasing age-sprecific prevalence of HIV-2 might indicate the former , in that HIV-2 appears to be the indigenous virus and HIV-1 entering typical high risk groups at greater frequency.

EPIDEMIOLOGIC PATTERNS OF HIV-2 AND HIV-1

PATTERN A: HIV-2

<1% GENERAL POPULATION
Less HIV-1; Ratio of HIV-2 to HIV-1 (>10)
e.g. SENEGAL, GAMBIA, CAPE VERDE

PATTERN B: HIV-2 HIGHLY ENDEMIC

5-10% HIV-2 GENERAL POPULATION
Less HIV-1
e.g. GUINEA BISSAU

PATTERN C: HIV-1 and HIV-2

1-10% of both viruses in general population
"DUAL REACTIVES" (cross-reactivity, dual exposure, dual infection)
e.g. BURKINA FASO, IVORY COAST

PATTERN D: HIV-2 LOW TO ABSENT

HIV-2 entering with travellers from HIV-2 endemic areas

A better understanding of these patterns and their significance will be possible, once the pathogenicity and transmission rate of HIV-2 is better understood. In addition, there is still the potential for varying biological properties amongst HIV-2 viruses which would also alter the chronological interpretation of such patterns. Finally, these patterns are useful in determining health policy towards HIV-2 infection. For the United States and Europe, the most likely high risk group for HIV-2 infection is those individuals with a link to an HIV-2 endemic country.

HIV-2 has been found at high rates in populations of West Africa where as yet high rates of AIDS cases have not been described. This has suggested that HIV-2 may differ in pathogenicity from HIV-1. In order to evaluate this on a population level the rate of transmission of the virus is important to determine. Through evaluation of sequential samples from a high risk group in Dakar, Senegal, we determined and characterized seroconversion in this population.

A population of 1300 registered female prostitutes have been followed with sequential serology since 1985. All serum samples were evaluated for antibodies to HIV-1 and HIV-2 by immunoblot.

14 women were found to seroconvert to HIV-2 with 22.6 person-years of observation. The mean time of observation prior to seroconversion was 17

months. At the time of seroconversion antibodies to the env gene products gp38-40 and gp105 for HIV-2(MS) were readily detected by immunoblot. 14/14 had antibodies to p24(gag), 13/14 to p66(pol), 11/14 to p51(pol), and 8/14 to p15(gag). HIV-2 seroconverters were compared to 1106 women (963 person-years) who remained seronegative. Risk factor analysis showed that seroconverters were significantly older than non-seroconverters ($p<.025$). Nationality or years of prostitution were not significant risk factors for seroconversion. None of the seroconverters developped AIDS or related signs. The seroconversion rate was found to be less than 2% based on 974 person-years of observation in this large high risk population.

Seroconversion for HIV-2 appears quite low despite over 10% prevalence in this high risk population. This suggests slow spread of HIV-2 in contrast to HIV-1 at a population level. This appears to parallel data on HIV-2 virus carriage within an individual. A number of laboratories have reported low efficiency at isolating HIV-2 virus from asymptomatic individuals, even in contrast to the isolation of HIV-1 from asymptomatics. In addition, the virus propogation appears quite slow, indicative of low virus titer in the original sample. HIV-2 isolates from AIDS patients has been more easily obtained but the relevance of studies on such isolates must be considered carefully. The major proportion of HIV-2 infected individuals identified thus far (several thousand) , appear to be free of clinical signs, more emphasis on the study of viruses from such people is needed.

Preliminary computer analysis of the risk factor analysis on the cohort study of HIV-2 infected prostitutes has been completed on the first 139 records. This represents a subset of the actual cohort being followed which presently

includes 150 HIV-2 positive women and 300 matched negatives; an additional 10 HIV-1+ or HIV-1/HIV-2+ women are also enrolled in the study. We were already aware that the matching criteria were associated with seropositivity including age, nationality and years of prostitution, these will be analyzed in the larger prostitute population which includes 1600 women. There was no significant association with previous hospitalization, transfusion, circumcision, scarification or tatooing. In additon, there was no difference between positives and negatives with respect to the number of children or mortality in infants or children. The only possible risk factor associated with seropositivity appears to be the number of lifetime sexual partners which would be consistent with the association of retrovirus carriage and sexual promiscuity.

NATURAL HISTORY OF HIV-2

We have followed a large group of registered female prostitutes (n>1300) in Dakar, Senegal to better understand the epidemiology of HIV-2. Since 1985, all women registered at the Institute Hygiene Sociale in Dakar, Senegal were enrolled in the study. Physical examinations, questionnaires regarding risk and sexual behavior were administered and serum samples obtained for STD and retrovirus examination semi-annually. Counselling and condom distribution began in late 1986 and data regarding efficacy of intervention was obtained subsequently.

As of early 1989 ,the overall seroprevalence in 1301 female prostitutes was 9.9% HIV-2, 1.2% HIV-1 and 0.5% HIV-1/2. The majority of women were native Senegalese (73%), with 21% from Ghana and 6% other nationalities. The mean age was 34 yrs, range 21-68, and the mean years of prostitution 6.7 yrs, range 1-19. HIV-2 positive prostitutes were more likely to be older (OR=2.58)

and to be non-Senegalese (OR=1.79). The number of years of prostitution was not significantly related to serostatus. Inclusion of all variables in a multivariate logistic model did not modify these results The spread of HIV-2 in this population was slow as judged by less than 2% seroconversion with 974 person-years of observation. History of transfusion, hospitalization, circumcision,tatooing and scarification were not found to be significant risk factors for HIV-2 infection. 120 person-years of follow-up on HIV-2 positive women has failed find evidence of the development of AIDS or related signs.

The epidemiology of HIV-2 in a high risk population followed over time appears to differ significantly from that of HIV-1. These differences include the risk factors for infection, rates of transmission and clinical outcome.

Since 1985 we have been involved in a Dakar female prostitute cohort study whereby 150 HIV-2 positive have been matched with 300 HIV-2 negative prostitutes on age, nationality and years of prostitution. These women are followed semi-annually with questionnaires, clinical evaluation, STD diagnostics and immunologic exam. Condom distribution and counselling began in late 1986.

There have been no cases of ARC or AIDS. Various minor health problems were not unique to either seropositive or seronegative groups. A subset of 71 seropostive and seronegative prostitutes have been analyzed from CBC and lymphocyte subset determinations. Controlling for age, nationality, years of prostitution and number of sexual partners per day; we performed a multivariate analysis to evaluate the various hematologic parameters in relation to serostatus. None of the HIV-2 seropositive women demonstrated T4 values in

the abnormal range (<500). A significant elevation in T8 cells was noted in seropostives after adjust ment for the above parameters.

	HIV-2+	HIV-2-
T4 <500 (Abnormal)	0	1
T4 > 500	27	43

*None of the HIV-2+ individuals demonstrated decreased T4 lymphocytes.

T8 (mean ± SD)	1237 ± 730	926 ± 372

*In multivariate analysis a significant elevation in T8 lymphocytes (p=.02) was noted in HIV-2 seropositives.

Natural History of AIDS and its association with HIVs

To evaluate the performance in Senegal of the provisional WHO clinical criteria for AIDS in developing countries, we surveyed suspected cases referred for serologic testing to Prof. M'Boup's laboratory from 1986 to the present. Cases suspected of AIDS had at least 2 of the major or minor signs in the WHO criteria.

Results: Serostatus	Suspected AIDS-like illness	WHO criteria fulfilled	% Suspected AIDS-like cases fulfilling WHO criteria
HIV-1	19	17	89.5
HIV-2	14	9	64.3
Both	4	3	75.0
Neither	61	24	39.3
Total:	98	53	54.1

The high rate of seronegative "AIDS" cases (almost half of all cases fulfilling the criteria) makes the evaluation of AIDS solely by these criteria difficult in this region. The larger number of HIV-1 associated AIDS cases is of interest, considering that HIV-1 is less prevalent than HIV-2 in this region. Extensive clinical surveys and perhaps distinct clinical criteria may have to be considered to survey disease association and HIV-2 exposure.

Perinatal Infection with HIV-2

The seroprevalence of HIV-2 in pregnant women in various urban centers in Senegal was determined by immunoblot on HIV-2 and HIV-1 antigens.

City	# of Samples	HIV-2%	HIV-1%
Pikine	220	0.4%	0%
Louga	184	1.1%	0%
Ziguinchor	550	1.1%	0%

Paired serum samples from mothers and heel-prick blood samples dried on filter paper from their infants (age= 1-24 months) were analyzed by immunoblot for antibodies to HIV-2 and HIV-1. 3 of 92 mother-infant pairs were found to be HIV-2 positive, none were HIV-1 positive. There was 100% concordance between HIV-2+ mothers and HIV-2+ infants. Clinical and immunologic studies of HIV-2+ infants are ongoing. These studies indicate that filter-paper eluates may be an effective means of detecting seropositivity in infants. This technique is a cost-effective means of surveillance for perinatal retroviral transmission in endemic areas.

HIV-2 Infection in children

Studies are presently underway in Kaolack, Senegal to evaluate prostitute children ages 2-12 years cross-sectionally. Questionnaire data and mother's serostatus will help evaluate other risk factors for HIV-2 positive children. Clinical examination and follow-up on a matched cohort of children will begin after cross-sectional data is compiled. Due to the low number of HIV-2 infected pregnant women accessible for a perinatal transmission study, we chose to look at children already borne to HIV-2 infected women. This design also allows for elimination of age groups, less than 2 years, which will suffer from a high mortality rate due to non-retroviral causes.

HIV-2 VIROLOGY

The humoral response to HIV-2 viral antigens also shows some interesting contrasts to that of HIV-1. There is a more consistent response to all of the major viral structural proteins and one unique subset of reactors that only appear to react with env-related antigens. This serologic patterns is highly associated with Portugese colony origin rather than French West Africa. The potential of strain variability must therefore be addressed, as mentionned earlier in the epidemiology section. The titer of anti-viral antibodies in HIV-2 is also quite high, in limited dilutions studies we believe this to be at least several logs higher than that of healthy asymptomatic HIV-1 sera. More extensive studies are needed on the serologic profiles to various HIV-2 regulatory proteins both cross-sectionally and prospectively to determine their role if any in the natural history of infection.

This study was conducted to evaluate the major viral antigens of multiple HIV-2 isolates originating from West Africa. Of particular interest, was the characterization of envelope-related glycoproteins and their antigenic reactivity. In addition, we wished to study the antibody response of HIV-2 infected individuals to HIV-2 antigens from various isolates. The viral antigens of 8 different HIV-2 isolates including: 289, ST, MS, AS, DIAW, TY, SBL-6669, and NIH-Z were compared by immunoblot and RIP-SDS/PAGE. Serum samples from HIV-2+ and HIV-2- individuals representing 7 different West African countries were analyzed by immunoblot for antibody profiles to these various HIV-2 isolates.

The majority of HIV-2 serum samples irrespective of geographic origin demonstrated a typical profile to HIV-2 antigens including the: gp160, gp120, gp32-40, p55, p24, p64, p53 and p34. These represent the major env, gag and pol antigens of these viruses. A minority of HIV-2 positive serum samples demonstrated reactivity only to the env-related glycoproteins, gp160, gp120 and gp32-40. All HIV-2 positive serum samples showed equal reactivity to the env, gag and pol antigens of multiple isolates. This indicates that serodiagnosis utilizing different HIV-2 strains as antigenic sources should be comparable.

ANTIBODY REACTIVITY TO DIFFERENT HIV-2 ISOLATES

	HIV-2 STRAIN		
ANTIBODY PROFILE:	289	MS	SBL-6669
gp120, gp160, gp32, p64, p53, p34, p55, p24	358/358 (100%)	358/358 (100%)	352/352 (100%)
gp120, gp160, gp32	22/22 (100%)	22/22 (100%)	22/22 (100%)
NEGATIVE	388/388 (100%)	388/388 (100%)	25/25 (100%)

Through ongoing epidemiologic and clinico-prospective studies we have ready access to materials for HIV-2 virus isolation or DNA for PCR analysis. We have now analyzed 10 different HIV-2 isolates. All the isolates are characterized by their antigenic relationship to prototype HIV-2 strains as well as their genetic homology as determined by Southern Blot hybridization with HIV-2 probes. RIP analysis of S35 cysteine labelled cell lysates have shown some polymorphism in major viral structural proteins that does not appear to be dependent on cell line origin. This has been extended with pulse chase studies and tunicamycin

inhibition to identify different sizes of the envelope precursor and mature products in each of these HIV-2 infected cell lines. Certain HIV-2 isolates such as ST have been shown with two different size transmembrane proteins including a gp32 and gp40. Despite polymorphism, the envelope antigens were the most immunogenic in all HIV-2 positive samples tested. We could not distinquish any strain-specific reactivity to the major viral antigens including the env-related glycoproteins.

Immunoblot of supernatant HIV-2 virus has shown polymorphism in the size of the transmembrane protein which may be due to the presence or modulation of a stop codon in the transmembrane envelope open reading frame. As yet, there has been no correlation between health status of the individual and/or geographic origin to the size of the transmembrane protein. In the future, we hope to use PCR technology to examine this in PBLs directly from the individual without culture, to rule-out the possibility that the stop codon is a product of in vitro cultivation and selection.

We have also analyzed these HIV-2 cell lines for their production of the vpx product, a unique regulatory gene of HIV-2. Utilizing heterologous anti-vpx sera we have found variable expression of the vpx product as well as extensive polymorphism in the vpx protein as analyzed by either RIP-SDS/PAGE or immunoblot. We presently detect anti-vpx antibodies utilizing virus preparations and have found relatively low rates of anti-vpx antibodies, less than 20%, depending on geographics and health status of the HIV-2 positive sera analyzed. We hope to extend these studies to better understand the role of anti-vpx in the natural history of HIV-2 infection, as well as its potential as a prognostic marker. Positive reactivity to vpx in "dual reactives" is useful in

establishing proof of active HIV-2 replication. Similarly, anti-vpu reactivity in "dual reactive" would also establish proof of active HIV-1 replication.

HIV-2 infectivity /CPE/ tropism in vitro studies

The ability of HIV viruses to infect specific cell lines and their effect on those lines is emerging as an important distinction between various strains. Initially named for their characteristic of being "human T–cell lymphotropic viruses", it was soon shown that other cell types could be infected, including macrophages, peripheral blood monocytes, B–cell lines, and T–cell lines. The ability to infect a given cell or cell line depends on the expression by the cell of the CD4 lymphocyte differentiation marker. Infected cells experience cytopathic effects characterized by cell fusion to form syncytia with cell killing. These cytopathic effects are also dependent on the presence of CD4 antigen, although more CD4 must be present in order to induce cell fusion than is necessary for infection.

HIV–2 isolates from West Africa have been reported with varying degrees of cytopathicity. LAV–2, (now called HIV–2ROD) isolated from a Cape Verde man with AIDS-like symptoms, was reported to be cytopathic towards the T-lymphocyte cell line HUT 78. Multinucleated giant cells and cell lysis were observed SBL6669, isolated from a Gambian woman with chronic respiratory infections, showed similar cytopathicity towards HUT-78. HIV-2UC1 was isolated from a patient in the Ivory Coast who had neurologic symptoms and multiple parasitic bowel infections. The isolate could productively infect, but was not cytopathic towards, the T–cell lines HUT 78 and SUPT1. It was unable, however, to infect the monocyte line U937, which can be infected with HIV–1.

HIV–2ST, isolated from a healthy Senegalese prostitute, was not cytopathic towards the T–cell lines HUT 78, H9, or SUPT1. Syncytia were not formed. There was "modest" cytopathic effect in the T–cell B–cell hybrid line CEM–174. The difficulty of isolating HIV–2 virus from healthy subjects has been noted.

Pelleted virus from various HIV-2 persistantly infected cell lines were was standardized for reverse transcriptase and inoculated onto polybrene-treated uninfected cell lines SupT-1 and U937. Infection was assayed every 3 days by fixed cell immunofluorescence and reverse transcriptase. Cytopathicity was evaluated by trypan blue exclusion and scoring for synctia cells. 500,000 cpm were inoculated onto a fixed number of uninfected cells and monitored for 3 weeks.

The following viruses were used,the cell lines to which the virus was adapted to is indicated. Southern blot analysis has demonstrated that these are all in fact HIV-2 viruses that differ from each other by restriction fragment analysis.

Virus	Health Status
1. TY In HUT78	sick
2. ID In SUPT1	healthy
3. MS In U937	died of AIDS
4. MS In SUPT1	died of AIDS
5. NIH-Z In SUPT1	AIDS
6. SBL6669 In SUPT1	respiratory infections
7. PK289 In HUT 78	healthy
8. HIV2-ST clone 24 In SUPT1	healthy

Infectivity and cytopathicity studies:

Virus	SUPT1		U937	
	Infects	Cytopathic	Infects	Cytopathic
1. DIAW/SUPT1	+	+	–	–
2. TY/HUT 78	+	–	–	+
3. HIV-2ST/SUPT1	+	–	–	–
4. LAV 2/SUPT1	+	+	+	+
5. MS/SUPT1	+	+	+	+
6. MS/U937	+	+	+	+
7. SBL6669/SUPT1	+	+	+	+
8. P289/HUT78	–	–	–	–

The results presented here are in concordance with the concept that viruses derived from sick individuals are more broadly infectious than virus from healthy persons infected with HIV-2. The exception, TY virus from a sick person exposed to virus 15 years ago, being unable to infect U937, must be qualified by the observation that the virus was cytopathic for U937. The ability of a given virus to get into a given line in this study does not indicate that a line is incapable of becoming infected with the virus. The intent here was not to force viruses into lines, but rather to gauge the relative infectivity of a standardized load of viruses. Standardization of dose by reverse transcriptase levels may not be a perfect indicator of infectious dose. In our laboratory, cell lines infected with SIV can have normal production of viral antigen detected by Western blot, yet have only background levels of reverse transcriptase activity . Ohta has noted the same effect in SIV infected HUT 78 . In this study, MS from SUPT1 was able to infect both SUPT1 and U937 readily despite an inoculum that was an order of magnitude lower by reverse transcriptase than the other viruses used. Though standardization between different strains may not be perfect using RT, for any given strain the inoculum put onto the different cell lines was identical.

Viruses adapted onto a given cell line are obviously more readily passed to that same cell line. In this study it appeared that MS virus grown in SUPT1 was adapted to that line, with an abiiity to reinfect SUPT1 more rapidly than U937 and greater cytopathic effect in SUPT1 relative to MS virus derived from the U937 culture. Attempts to understand pathogenicity in humans by studying virus cultured in cell lines must consider the skewing effects of these adaptations.

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