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TITLE: BIOLOGICAL CHARACTERIZATION OF HIV-2

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13. ABSTRACT *(Maximum 200 words)*

Our data on the biology of HIV-2 suggest that this virus has a distinct biology from that of its closest relative HIV-1. It was therefore relevant to assess these differences in populations infected with significant rates of both HIV-2 and HIV-1. Senegal is such a West African country, and the studies established there have provided important new information on the natural history and epidemiology of HIV-2. The prolonged incubation period for HIVs in general suggest that much can be learned from the evaluation of infected individuals over time. In this contract we have described differences in the heterosexual transmission, incubation period to disease and epidemic curves of HIV-2 compared to HIV-1. A number of virologic and immunologic differences between these viral infections have been described which may play a role in these different pathogenic potentials and biologics. Our studies conducted to date, have already indicted differences in the above virus-host interactions between HIV-2 and HIV-1. Continued comparative studies contribute to our overall understanding of HIV pathogenesis.

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FOREWORD

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PJK **For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45 CFR 46.**

PJK **In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.**

PI Signature Phyllis J. Kanki **Date** 3/28/94

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FINAL FINANCIAL REPORT

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3. Reporting period from 09/28/90 to 02/27/94

4. PI Dr. Phyllis J. Kanki 5. Telephone No. (617) 432-1267

6. Institution Harvard School of Public Health, Dept. Cancer Biology

7. Project Title: Biological Characterization of HIV-2

8. Current staff, with percent effort of each on project.

Dr. Phyllis J. Kanki	75%	Leigh Remington	100%
Dr. Richard Marlink	5%	Christopher Mullins	50%
Geoffrey Eisen	50%	Karyn Ingram	25%
Er Zhang	100%	Don Hamel	100%

9. Contract expenditures to date:

Personnel	701,065.87	Supplies	137,935.40
Travel	62,852.00	Subcontract	190,155.00
Equipment	36,390.77	Publishing	7,242.79
		TOTAL DIRECT COSTS:	$1,135,641.83

10. Comments on administrative and logistical matters.

Dr. Marlink reduced his effort to 5% in the latter months of this contract, and a portion of his salary and fringe benefits were removed to reflect actual effort on the project. We also reduced the amount spent on travel because the Fogarty International Training Program funded a workshop in Dakar, and we were able to combine one of the collaborative scientific visits to the subcontractor with that workshop. We were allowed to bill a large portion of the airfare for that trip to the other project, resulting in a reduction in the travel expenditure reported in December, 1993. Our obligation for supplies on this project as of 09/27/93 was $139,104.32, but there were insufficient funds available to meet this obligation, and only $137,935.40 is therefore being billed against contract funds for these supplies.

11. Use additional page(s), as necessary, to describe scientific progress for the quarter in terms of the tasks or objectives listed in the statement of work for this contract. Explain deviations where this isn't possible. Include data where possible.

12. Use additional page(s) to present a brief statement of plans or milestones for the next quarter.

INTRODUCTION

Over the past decade our appreciation of the biological diversity of human and animal retroviruses has increased dramatically. The Human Immunodeficiency Virus type 1 (HIV-1) is now well-recognized as the cause of Acquired Immunodeficiency Syndrome (AIDS) which has reached epidemic proportions in many countries worldwide. In 1985, healthy Senegalese female prostitutes were reported to have antibodies highly reactive with SIV, a recently described simian virus related to HIV-1 (1,2). This data was suggestive of a new human retrovirus more closely related to SIV and more distantly related to HIV-1. Subsequent isolation and characterization of viruses from other West Africans confirmed these findings and the virus has been termed Human Immunodeficiency Virus type 2 (HIV-2). (3-5) Early reports of HIV-2 were from AIDS patients and fears of a second AIDS pandemic were raised.

HIV-2 was given its name to indicate its close relationship to HIV-1, the prototype AIDS virus. This was based on similarities in cell tropism, major antigenic cross-reactivity and genetic properties. Despite the similarities of HIV-2 to HIV-1 from a virological standpoint, many aspects of the comparative epidemiology of these two human retroviruses are still incompletely understood. Seroepidemiologic studies have demonstrated significant rates of HIV-2 infection in West Africa, and case reports from the US and Europe indicate that the spread of HIV-2 through international travel is ongoing (5-14). It is therefore of critical importance to better understand the biology and clinical significance of HIV-2 infection and evaluate its potential as a second AIDS causing virus.

Since the discovery of HIV-2 we have been involved in a clinical prospective study of registered female prostitutes in Senegal . These studies have shown that HIV-2 may be distinct from HIV-1 in more than its geographic distribution in Africa. Our first objective for this contract has been to characterize the epidemiology and natural history of HIV-2. Three epidemiologic cohort studies of female prostitutes in Senegal have been established and evaluated for seroprevalence, seroincidence and identification of risk factors for HIV-2 and HIV-1 infection (15-18). Sub-cohorts from each site have been monitored for clinical and immunologic abnormalities to characterize the natural history of HIV-2 infection (16,19). This is a unique study population with both HIV virus types and the longest and largest prospective study of HIV infected individuals conducted in Africa.

Our second objective has been to characterize the immunologic response to HIV-2 and assess its relationship to viral load and disease progression. We have strived to identify quantitative or qualitative differences in HIV-2 antibody responses to viral structural and regulatory proteins, assess correlation with health status, time of infection and geographic origin. Virus isolation and characterization and PCR studies are in progress to assess quantitative and qualitative differences that may correlate with the natural history of HIV-2 infection.

Objective 1:
Epidemiology and Natural History of HIV-2

Our first serologic studies in Senegal in 1985 demonstrated HIV-2 antibodies in healthy female registered prostitutes from the capital city, Dakar (2,6). To further evaluate the extent of HIV-2 infection in this sexually active high risk group we surveyed other registered female prostitute populations in other parts of the country. The seroprevalence for HIV-2 varied widely between six different registered prostitute populations in various urban centers throughout Senegal (n=1920): Ziguinchor (46.2 percent), Kaolack (28.8 percent), Louga (21.4 percent), Dakar (9.8 percent), Thies (4.6 percent) and St. Louis (1.5 percent) (5,15). These data suggested that even within a self-identified high risk group, risk factors associated with HIV-2 seropositivity might vary considerably. The current study was undertaken to identify and compare the risk determinants for HIV-2 in three populations of female registered prostitutes from Dakar, Ziguinchor, and Kaolack.

In 1970, the government of the Republic of Senegal instituted a program for the registration of self-identified female prostitutes, legalizing their practice of providing sex for payment. This program required semi-annual evaluation and treatment if necessary for sexually transmitted diseases at clinic centers established for this purpose in Dakar (1970), Kaolack (1987), and Ziguinchor (1987). Venous blood samples were routinely taken at annual intervals to assess serologic status. These centers originally managed by social workers and nurse practitioners were joined by our study physicians in Dakar (1985), Kaolack (1987) and Ziguinchor (1987). This allowed for a more complete physical examination but also more extensive clinical assessment at scheduled and non-scheduled visits. All registered prostitutes visiting the clinics were asked to participate in the study and have their blood tested for HIV. All registered prostitutes consenting to participate, with at least one serum sampling, were included in the study, beginning in Dakar in 1985, Ziguinchor and Kaolack in 1987, with all current and subsequently registered prostitutes enrolled until December, 1990.

Risk determinants of HIV-2 and HIV-1 *(Prevalence and Risk Determinants of HIV-2 and HIV-1 in West African Female Prostitutes Am. J. of Epi. 136 (7) 895-907) 1992 (17)*

The multi-site design of the study was implemented in order to evaluate HIV-2 infection in multiple cohorts with distinct demographic and behavioral characteristics (Table 1). Each cohort showed a distinct distribution of nationalities, with the major portion being Senegalese. In Dakar, 24.8 percent (316/1275) of the registered prostitutes were non-Senegalese nationality, two-thirds of these women were Ghanian (67.4 percent; 213/316). In Ziguinchor, 39.6 percent (110/278) were non-Senegalese, the vast majority of which were from Guinea Bissau (90.9 percent; 100/110). Kaolack was the only cohort composed largely of Senegalese women (98.1 percent; 154/157).

Senegal, similar to many other African countries, is characterized by a population comprised of a large number of distinct ethnic groups, frequently speaking a distinct language. Over 20 different ethnic groups were represented in our three different cohorts of registered prostitutes. These were collapsed into ten basic groups based on known ethnologic data, as follows: 1) Wolof, 2) Serere, 3) Peuhl, 4) Toucouleur, 5) Mandinque, Bambara, Soce, Sarankole, Dialancke and Soussou, 6) Mandjaque, Pepelle and Mancagne, 7) Diola, 8) Maure, Lebou, Balante, and Cariviano, 9) Ashanti and 10) Krobo. The latter two ethnic groupings represent major ethnic groups among Ghanians only. Preliminary analysis of ethnic group demonstrated an association to serostatus, cohort site, and various traditional skin-piercing practices. It was therefore decided *a priori* that this variable would be an important risk factor and was included in the logistic regression core model.

All three study sites had significant HIV-2 infection over their respective study periods; Dakar 10.0 percent (128/1275), Ziguinchor 38.1 percent (106/278) and Kaolack 27.4 percent (43/157) (table 2). The HIV-1 prevalence was most significant in Dakar, 4.1 percent (52/1275). The HIV-1 prevalence in Ziguinchor was 0.4 percent (1/278) and 1.3 percent (2/157) in Kaolack. In Dakar, a total of five women had serologic profiles consistent with dual reactive status based on immunoblot and/or reactivity to HIV-1 vpu or HIV-2 vpx (17-19).

TABLE 1. *Demographic characteristics of registered female prostitutes by Human Immunodeficiency Virus type 1 (HIV-1) and type 2 (HIV-2) in Dakar, Ziguinchor and Kaolack, Senegal, 1985-1990.*

Population Characteristics	Dakar			Ziguinchor			Kaolack		
	No.*	% HIV-2 seropositive†	% HIV-1 seropositive	No.	% HIV-2 seropositive	% HIV-1 seropositive	No.	% HIV-2 seropositive	% HIV-1 seropositive
Study population	1275	10.0	4.1	278	38.1	0.4	157	27.4	1.3
Nationality									
Senegal	959	9.2	2.4	168	25.7	0.6	154	27.9	1.3
Ghana	213	13.2	9.8	5	0.0	0.0	0	0.0	0.0
Guinea Bissau	12	50.0	0.0	100	60.0	0.0	2	(1/2)	0.0
Other Nationalities	91	6.6	8.8	5	(1/5)‡	0.0	1	0.0	0.0
Age (years)									
20-29	350	7.4	4.6	74	23.0	0.0	32	12.5	0.0
30-39	655	9.3	4.1	141	38.3	0.0	85	22.3	1.2
40-49	225	12.0	4.0	45	51.1	2.2	29	44.8	3.4
50-59	40	27.5	0.0	14	64.3	0.0	10	(7/10)	0.0
60-69	5	(3/5)	0.0	2	(1/2)	0.0	1	(1/1)	0.0
Years of registered prostitution									
1-9	902	9.9	5.2	278	38.1	0.4	106	23.6	1.9
10-19	351	10.0	1.4	0	0.0	0.0	51	37.2	0.0
20-29	22	18.2	0.0	0	0.0	0.0	0	0.0	0.0
Years of sexual activity									
0-9	122	4.9	8.2	26	19.2	0.0	5	(1/5)	0.0
10-19	553	8.3	4.5	95	29.5	0.0	57	15.8	0.0
20-29	386	9.8	3.4	62	41.9	1.6	41	31.7	4.9
30-39	70	14.3	0.0	19	57.9	0.0	17	70.6	0.0
40-49	13	61.5	0.0	3	(2/3)	0.0	5	(4/5)	0.0

* No., number of prostitutes with characteristic, this serves as denominator of the percentage for each stratum. Dual reactives removed.

†%, percentage of prostitutes with characteristic and seropositive by stratum.

‡ ( ), raw proportion for small numbers.

Step-up logistic-regression analysis of the Dakar cohort data revealed that a history of traditional scarification was positively associated with HIV-2 infection (Adjusted OR=1.65, 95 percent CI=1.06-2.57) (Table 2). In addition, increased years of sexual activity was also found to be a positive risk factor for HIV-2 infection (for each 1-year of increase the adjusted OR=1.05, 95 percent CI=1.02-1.08). Risk determinants for HIV-1 infection in the Dakar cohort differed markedly from risk determinants for HIV-2 infection. Logistic regression analysis revealed an increased risk of HIV-1 seropositivity for individuals reporting a history of hospitalization (Adjusted OR=2.12, 95 percent CI=1.11-4.03) . A shorter period of registered prostitution was also found to be associated with HIV-1 infection (Adjusted OR= 0.86, 95 percent CI= 0.79-0.95).

In the Ziguinchor study group, 36 percent of the women were from Guinea Bissau, a country with high prevalence of HIV-2 (table 1) (6,15,20,21). In analysis of this cohort, HIV-2 seropositivity was highly associated with women of Guinea Bissau nationality (Adjusted OR=6.27, CI=1.43-27.59), despite controlling for ethnic groups. Again, increased years of sexual activity was significantly associated with HIV-2 infection (Adjusted OR= 1.06, 95 percent CI= 1.01-1.12). In contrast to the Dakar cohort, a relatively low prevalence of HIV-1 infection was found (0.7 percent). Due to the small number of HIV-1 infected women, evaluation of risk determinants for HIV-1 in this cohort was not performed.

Similar to the other two cohorts, risk determinants for HIV-2 infection in the Kaolack cohort included increased years of sexual activity (Adjusted OR= 1.11, 95 percent CI= 1.04-1.18). History of always or sometimes using condoms was found to be protective for HIV-2 infection (Adjusted OR= 0.27, 95 percent CI= 0.09-0.82). The prevalence of HIV-1 was low (1.3 percent), therefore, evaluation of HIV-1 risk determinants in this cohort was not performed.

The final analysis for risk determinants of HIV-2 infection was conducted on Senegalese prostitutes pooled from all three cohort sites (n=1280). Women of non-Senegalese nationality were excluded since cohort specific analysis had already indicated that nationality was a significant risk factor for HIV infection. It was also hypothesized that risk determinants in non-Senegalese women would be more heterogeneous and obscure the analysis. In addition, since the preponderance of HIV-1 infected women were from the Dakar cohort, analysis was limited to evaluation of risk determinants for HIV-2 infection.

TABLE 2. Risk determinants associated with HIVs in Dakar, Ziguinchor, Kaolack, and Senegalese prostitutes from all three sites.

Study Site	HIV Type	Risk Determinant	Odds Ratio*	95% CI †	Risk Association
Dakar	HIV-2	Years of sexual activity	1.05	1.02-1.08	Increased
		History of scarification	1.65	1.06-2.57	Increased
Dakar	HIV-1	Years of registered prostitution	0.86	0.79-0.96	Decreased
		History of hospitalization	2.12	1.11-4.03	Increased
Ziguinchor	HIV-2	Years of sexual activity	1.06	1.01-1.12	Increased
		Guinea Bissau nationality	6.27	1.43-27.59	Increased
Kaolack	HIV-2	Years of sexual activity	1.11	1.03-1.18	Increased
		History of condom use	0.27	0.08-0.82	Decreased
All Senegalese prostitutes (3 sites)	HIV-2	Site (Ziguinchor)3.99	2.30-6.91	Increased	
		Site (Kaolack) 4.72	2.79-7.99	Increased	
		Years of sexual activity	1.07	1.05-1.10	Increased
		History of excision	0.47	0.27-0.85	Decreased
		History of BCG vaccination	0.53	0.29-0.95	Decreased

* Odds ratios were calculated by multiple logistic analysis. Odds ratio for a single variable, adjusting for ethnic group in the core model. † CI, confidence interval.

Multivariate analysis of the Senegalese prostitutes from all three sites revealed a number of risk determinants associated with HIV-2 infection (Table 2). Controlling for ethnic group, women from the Ziguinchor (Adjusted OR= 4.72, 95 percent CI=2.79-7.99) and Kaolack cohorts (Adjusted OR= 3.99, 95 percent CI =2.31-6.91) were much more likely to be HIV-2 positive as compared to women from the Dakar cohort. As had been demonstrated in the site-specific analysis, increased years of sexual activity was associated with HIV-2 seropositivity (Adjusted OR=1.07, 95 percent CI =1.05-1.10). History of excision was associated with a decreased risk of HIV-2 infection (Adjusted OR=0.47, 95 percent CI=0.27-0.85). Similarly, a previous history of BCG vaccination appeared to decrease the risk for HIV-2 seropositivity (Adjusted OR=0.53, 95 percent CI=0.29-0.95).

Stepwise logistic-regression analysis of the data revealed different risk determinants by study site and HIV virus type. The final analysis for risk determinants of HIV-2 infection was conducted on Senegalese prostitutes pooled from all three cohort sites (n=1280). Certain risk determinants that were found to be associated with HIV infection are difficult to interpret.

It is possible that many of these are linked to sexual practices including client selection. More in-depth data on the sexual behavior of these women would be necessary to pursue these findings.

In Africa, it has been well recognized that heterosexual transmission is a major mode of HIV infection. Cross-sectional studies of sexually active risk groups such as self-identified female prostitutes have consistently demonstrated high prevalence rates of both HIVs as compared to low-risk sentinel groups (15). We have therefore assumed that the major risk factor for the women in our studies is that of increased sexual activity. It could be hypothesized that age, years of registered prostitution, number of sexual partners per week and years of sexual activity might all be variables that measure degree of potential sexual exposure to HIV. Multivariate analysis of the three cohorts as well as the pooled Senegalese cohort showed that women with more years of sexual activity were more likely to be HIV-2 seropositive. The approximate log-linear relationship of HIV-2 seropositivity with increasing years of sexual activity is consistent with the hypothesis that this virus has been in this population for at least several decades. The potential cohort effect that might produce this result, namely a recent decrease in HIV-2 prevalence, is unlikely, given the stable incidence rate of HIV-2 since 1985 (18).

In distinct contrast to these results, women with fewer years of registered prostitution were more likely to be HIV-1 infected. It is not known why women with a shorter duration of practicing prostitution were at higher risk for HIV-1 infection. Similar results have also been reported in HIV-1 seropositive prostitutes in Nairobi, Kenya (22). It is conceivable that client selection and sexual practices may change during the practice of prostitution. Similarly, a woman may be more prone to active infection by other STD agents early in her prostitution career, which may increase susceptibility to HIV-1 infection. Finally, a recent increasing HIV-1 prevalence or cohort effect may be responsible for this association of HIV-1 to shorter duration of prostitution. This is substantiated by data from an incidence study conducted in this same cohort, described below (18). The data suggest that there is a difference in the potential risk of acquiring HIV-1 as compared to HIV-2 infection via the sexual route

The use of a government based existing mechanism for registered female prostitutes allowed for a relatively uniform sampling frame in all three sites. However, participation in this study was voluntary, with 67.5 percent participation in Dakar, 83.7 percent in Ziguinchor and 72.3 percent in Kaolack. The distribution of HIV serostatus, nationality, age, and years of registered prostitution were very similar between enrolled and non-enrolled women at all

sites (data not shown). Therefore, study cohorts were considered representative of the registered prostitute populations at the designated sites.

A number of studies have indicated an association between HIV infection and other STDs, particularly those involving genital ulceration (22, 23). In sexually active risk groups, an association between HIV infection and STDs is not unexpected. However, in cross-sectional studies, it is difficult to determine whether the STD agent or agents serves as a risk factor for acquisition of HIV infection or as a co-factor in the natural history of HIV infection. Condom distribution and counselling on the prevention of STDs may be considered an intervention for both HIV and STD acquisition. The temporal effectiveness of this intervention was not assessed in this study, and would lead to difficulties in interpretation. This study was not designed to evaluate the role of STDS in HIV infection, these complex interactions are better addressed through specifically designed longitudinal studies.

Incidence Trends of HIV-1 and HIV-2 Infection *(Slower heterosexual spread of HIV-2 compared with HIV-1, Lancet, in press (18))*

Our prospective studies conducted in the Dakar cohort have provided the unique opportunity of measuring the incidence of both HIV-1 and HIV-2 in 1277 registered female prostitutes followed from 1985 to 1993. Over the 8 year study, 5608 samples from 1452 women with sequential serology were analyzed. Women entering the cohort with an initial seropositive result were followed with sequential serology, but were excluded from incidence estimates. The overall prevalence of HIV-2 was 11.3% (164/1452), with 6.2% prevalence of HIV-1 (90/1452) and 0.8% prevalence of dually reactive to both HIVs (12/1452). 1277 women with an initial seronegative sample were evaluated for seroconversion with a total of 4141 pyo over the 8 year period.

The overall incidence of HIV-2 infection in these women was 1.11 per 100 pyo, and that of HIV-1 infection was also 1.11 per 100 pyo; with annual incidence rates for both virus types shown on Table 3. HIV-1 annual incidence rose dramatically from 0 per 100 pyo in 1985-86 to 2.19 per 100 pyo in 1992 (95% Confidence interval = 0.98-4.87). HIV-2 annual incidence was relatively stable and this was confirmed by a relatively constant prevalence of HIV-2 throughout the study period (data not shown). We have previously reported an increase in HIV-2 age-specific prevalence indicative of a virus that has been present in the population for at least several decades (5,15). The stable incidence trend supports the hypothesis that HIV-2 is not a new infectious agent in this population and that its spread via sexual transmission is now relatively constant. Although this population is clearly experiencing new infections by

both HIVs, the data indicates that HIV-2 spread is leveling and that HIV-1 is the more recent and increasing source of HIV infection. The data suggests distinct differences in the relative infectivity and heterosexual transmission of HIV-2 as compared to HIV-1.

In order to evaluate changes in the risk of HIV-2 or HIV-1 infection during the study period, we obtained estimates for the increased risk associated with each additional calendar year of exposure. The estimates were obtained while simultaneously adjusting for age, nationality, years of registered prostitution, calendar year, and time in the study. The relative risk for HIV-2 infection associated with a subject entering a new calendar year from the previous one was not significant (relative risk, 1.04, 95% confidence interval, 0.89-1.21). There was, however, a significant trend for increasing risk of HIV-1 infection during the study period with a relative risk of 1.43 (p value<0.002, 95% confidence interval, 1.15-1.78) associated with movement from one year to the next. This suggested that the risk of HIV-1 infection increased 12-fold over the 8 year study period. Time in the study had no independent effect on the risk of seroconversion to either HIV-1 or HIV-2.

In areas of the world where the major mode of virus spread is via heterosexual transmission, incidence studies have been rarely conducted. A study of female prostitutes in Nairobi, Kenya has previously reported an HIV-1 seroincidence rate of 47% (total pyo= 176) (22), this being significantly higher than the rate seen in our study. There are a number of possible explanations for these differences. The prevalence of HIV-1 in our cohort was significantly lower than that of the Nairobi cohort, which is currently at close to 95% infection. Our incidence estimates are based on a significantly larger denominator of 4141 person-years, with narrow confidence intervals indicating relative lack of imprecision. In addition, the women in our study were regularly evaluated for sexually transmitted diseases and counseled on HIV prevention as part of the study design, which may have resulted in lower incidence rates. Nonetheless, despite the potential underestimation of HIV incidence, the noted differences in HIV-1 and HIV-2 incidence trends would still be valid.

The decreased transmissibility of HIV-2 relative to HIV-1 in these studies may reflect a lower infectivity of HIV-2. This hypothesis supports the observations of longer incubation period and lower incidence of HIV-2 AIDS compared to HIV-1 AIDS (16,19). Not only is this the only study of HIV-2 incidence but is one of the longest followed cohorts for incidence of HIV-1. The continued study of the incidence of HIV-1 and HIV-2 in this population will provide a unique opportunity for direct comparison of the spread of these two viruses. In addition, the

availability of such long-term incidence data will allow more precise predictions of future incidence rates and this data is critical to the ultimate success of Phase III efficacy trials.

Table 3: Annual incidence of HIV-1 and HIV-2 in registered female prostitutes in Dakar, Senegal

	Calendar Year	PYO*	HIV-2 Number of Seroconverters	HIV-2 Incidence Rate per 100 PYO (95% CI)	HIV-1 Number of Seroconverters	HIV-1 Incidence Rate per 100 PYO (95% CI)
1)	1985	187	2	1.07 (0.27-4.28)	0	0
2)	1986	448	5	1.12 (0.46-2.68)	0	0
3)	1987	552	5	0.91 (0.38-2.18)	4	0.72 (0.27-1.93)
4)	1988	609	4	0.66 (0.25-1.75)	4	0.66 (0.25-1.75)
5)	1989	704	8	1.14 (0.57-2.27)	5	0.71 (0.30-1.71)
6)	1990	732	12	1.64 (0.93-2.89)	9	1.23 (0.64-2.36)
7)	1991	640	8	1.25 (0.63-2.50)	18	2.81 (1.77-4.47)
8)	1992	274	2	0.73 (0.18-2.92)	6	2.19 (0.98-4.87)
			Overall Incidence			
	2/85-1/93	4141	46	1.11 (0.83-1.48)	46	1.11 (0.83-1.48)

Mathematical Model of HIV-1 and HIV-2 Transmission

(Comparison of Transmission Rates of HIV-1 and HIV-2 in a Cohort of Prostitutes in Senegal. Bull. Math. Bio., 55(4):731-41 (1993) (24)).

We have modeled the probability of male to female transmission of either HIV-1 or HIV-2 as a function of the number of sexual partners, the prevalence of the virus types and the infectivity per contact. Using maximum likelihood estimate theory and data from the Dakar cohort, we estimated and compared the infectivities of HIV-1 and HIV-2. Given a number of simplifying assumptions, the estimates of infectivity indicate that HIV-1 is 5-9-fold more infectious than HIV-2 per sexual act (24).

Natural History of HIV-2- *(Reduced Rate of Disease Development with HIV-2 compared to HIV-1, manuscript submitted for publication (11)).*

This report compares the immune alterations and the rate of disease development between HIV-2 and HIV-1 in this population (16,19). Cohort members were derived from women attending the "Institut d'Hygiène Sociale" (IHS) government sponsored health clinics for self-identified prostitutes in Dakar, Senegal. Since 1985, all adult women registered in the IHS clinic have been serologically screened for exposure to HIV-1 and HIV-2. The IHS provides clinical examinations, treatment of sexually transmitted disease (STDs) and primary health care during visits which are required every 6-8 weeks for the legal registration of prostitutes. We augmented the health evaluation and services at this clinic with specially trained study physicians, educational materials, condoms, diagnostic supplies, and medications.

Throughout each year during an initial IHS clinic visit, women were assigned a unique identification number and a blood sample for HIV testing was obtained with informed consent. A demographic, behavioral and health history questionnaire, and a baseline health evaluation was performed by clinic physicians and nurse practitioners. When women returned for subsequent clinic visits, all who tested HIV seropositive were enrolled in our clinical cohort with their consent. Two seronegative comparison women were selected for each eligible seropositive woman by distribution sampling based on age (±2 years), nationality, and years of registered prostitution (±3 years). That is, when a seropositive woman was identified, two similar seronegative women were randomly selected from a strata of comparable women. As with the seropositive women, these women became eligible for enrollment upon subsequent clinic visits. Twice a year, lists of the eligible enrollees for the clinical cohort were generated and distributed to the IHS clinic staff who identified enrollees as they returned for visits.

At the time of enrollment, and at subsequent biannual visits, participants were examined by a study physician and a blood sample was requested. The women were also administered a more extensive questionnaire in the language of their choice focusing on sexual history, contraception, as well as antecedent medical, pregnancy and child health data. A complete physical examination was performed and included the individual's weight, vital signs, 4-8 specific data entries for each "organ system" which emphasized signs or symptoms of opportunistic infections or of neurological compromise, and entries for any other significant clinical history or signs found during the consultation. Data was also available from a

gynecological exam, a cervical smear, and a general medical evaluation performed approximately every 6-8 weeks by nurse practitioners during routine IHS visits. Microbiological testing of endocervical swabs were performed as needed for diagnosis. The serological status was unknown to the on-site physician, but was available to any of the participating women on a confidential basis. All clinic patients were given condoms and information on preventing STDs. Additional diagnostic testing, medications or special clinic referrals were routinely provided as needed.

Information on women who did not return to the IHS clinic sites for a 12 month period was actively sought in the community via nurse practitioners, social workers, and physicians. Once a year a separate "lost to follow-up" data form was completed for each subject who was not seen during that year. This information included a clinical consultation at the subject's home or at another IHS clinic site, a basic follow-up visit (outside the clinic) noting health status and reasons for not returning to the clinic, or interviews with friends or family members concerning the subject's last known health status and new address, if relocated. Subjects were removed from the study if they expressed a desire to discontinue participation, if they had permanently moved out of the country, or if they had died.

Study subjects had biannual blood samples drawn for serological determination of HIV-1 and HIV-2 exposure. All sera were tested for antibodies to each virus by immunoblot in two laboratories: the Microbiology and Virology Department at Le Dantec Hospital in Dakar and the Department of Cancer Biology at the Harvard School of Public Health in Boston. Serostatus of each serum sample was determined according to the WHO consensus recommendations of the HIV-2 Working Group (25). Dual reactive sera to HIV-1 and HIV-2 were further confirmed by appropriate reactivity to type-specific synthetic peptides to the transmembrane glycoprotein regions of each virus type, as well as by radioimmunoprecipitation assay (RIPA). Reactivity to HTLV was determined by immunoblot reactivity to an HTLV cell lysate preparation in a cross-sectional sample of the study population.

Serological evaluation of antibodies to treponemal antigens was determined biannually by Treponemal Hemagglutination Assay (TPHA) and by Rapid Plasmin Reagent (RPR) determinations. Chlamydia antibodies were determined by Chlamydiazyme ELISA determinations (Abbott Labs). Gonococcal smears and cultures, as well as wet preps and potassium hydroxide preps for microscopic examination were performed, as needed for diagnosis.

In addition to the biannual clinical consultations and serological determinations, additional blood samples were requested on a yearly basis to determine a subject's's complete blood count (CBC) and T-cell subsets. Ethylenediaminetetraacetic acid (EDTA) anticoagulated blood was obtained and CBCs were determined by an automated cell counter (Coulter). Manual white blood cell differentials were obtained by averaging two readings. Peripheral blood mononuclear cells (PBMCs) were prepared for subset analysis by Ficoll-Hypaque-like separation via Leukoprep cell separation tubes (Becton Dickinson). Subpopulations of lymphocytes were identified by two-color fluorescence which utilized Leu-4 (CD3) and Leu-12 (CD19) for T and B cells respectively, or Leu-3a (CD4) and Leu-2a (CD8) for T4 and T8 cells respectively. Only lymphocytes with surface (ringed) staining were counted fluorescence microscopy. Monocytes and cells with cytoplasmic staining were excluded. The absolute subset counts were calculated by multiplying the percentage of lymphocyte subsets by the total number of lymphocytes. Inter-run variations of our technique were periodically determined by blood samples from multiple seronegative controls run simultaneously in triplicate.

Baseline tests determined that approximately 85% of our clinic population reacted to tuberculin antigen by multiple antigen skin testing (Multitest IMC, Merieux Institute, Paris). As a result, delayed type hypersensitivity skin testing to intradermal tuberculin antigen (ppd; Sclavo) was initiated on a yearly basis. Skin test reactions were read at 48 hours, and the extent of induration was recorded. Reactions were classified according to the manufacturers recommendations of reactive, limited reaction, or non-reactive.

AIDS was initially defined in our population according to the World Health Organization (WHO) conference on AIDS in Bangui (25). The major clinical signs are weight loss (at least 10% of body weight), chronic fever (intermittent or constant lasting at least one month) or chronic diarrhea (lasting at least one month). Minor clinical signs or symptoms are a persistent cough (lasting at least one month), pruritic maculopapular dermatitis, herpes zoster, oral candidiasis, chronic herpetic infection (progressive or disseminated) and generalized lymphadenopathy. In our study, AIDS was diagnosed when two major signs and at least one minor clinical sign was present. The presence of either Kaposi's sarcoma or cryptococcal meningitis alone was sufficient for an AIDS diagnosis by these recommendations.

Since HIV serology, T-cell subset determination and certain opportunistic infection diagnostic capabilities were available, our study population was also evaluated by the Centers for Disease Control (CDC) revised surveillance case definition for AIDS (26) and by the CDC Classification System for HIV Infection (27). All of the "WHO-defined" AIDS cases also corresponded to the CDC definition of AIDS. Cases which corresponded to the CDC IV disease classification that were not defined as AIDS by either WHO or CDC criteria (CDC IVA or C-2) were evaluated separately from and combined with the AIDS cases in the analysis.

In addition to evaluating the study population by these definitions, we also gathered clinical data on other possible HIV-associated outcomes at each clinical consultation. This data was historical, physical and diagnostic in nature. The examining physician was blind to the serological status of the subject when seen as an outpatient. Other clinical states evaluated included mucocutaneous manifestations (e.g. oral ulcerations, angular chelitis, minor mycotic infections, prurigo), recurrent or severe respiratory infections, global or localized neurological findings, and an overall performance status evaluation.

Statistical differences in percent seropositivity were evaluated using the Chi-square test or Fisher's exact test. Differences in continuous variables were evaluated by the t-test and Wilcoxon's test. Incidence rates, rate ratios and 95% confidence intervals were calculated for each outcome of interest. Incidence rate confidence intervals were calculated assuming a Poisson distribution. Seroincident cases that had estimated dates of seroconversion less than 18 months prior to the most recent clinical consultation were excluded as seropositive cases for this analysis. Only subjects who were initially asymptomatic according to our defined outcomes were included in this analysis. Person-years of observation (PYO) for each subject was determined by calculating the time from the initial basic health evaluation and serostatus determination until the most recent clinical consultation or removal from the study. We are assuming under this determination of PYO that a significant HIV-associated outcome, such as CDC IV-type disease, did not occur yet remain undetected between the initial clinic health evaluation with serostatus determination and the enrollment visit with our study physician. This assumption was validated by reviewing the subjects' clinic records and by obtaining a full medical history upon enrollment.

From February 1985 to December 1993, 78 HIV-1 seropositive women were enrolled, of whom 32 were seroincident and 46 were seroprevalent. In addition, 136 HIV-2 seropositive women were enrolled, of whom 33 were seroincident and 103 were seroprevalent. Twelve women dually reactive to HIV-1 and HIV-2 by all serologic criteria and 348 seronegative

comparison women were enrolled. The mean age of the enrolled cohort was 37 ± 7 years, with no significant difference between HIV-1 and HIV-2 seroincident enrollees. HIV-1 seroprevalent enrollees were slightly younger than the other groups with a mean age of 34 ± 6 years. In general, enrollees were officially registered as prostitutes 4 to 8 years prior to enrollment and had been sexually active since 16 to 17 years of age. Due to the distribution sampling of seronegative comparison enrollees, HIV-1 and HIV-2 seropositive women were similar to seronegative women in terms of age, years of registered prostitution, and nationality.

At the beginning of each calendar year, study physicians and social workers actively investigated enrollees who had not attended the clinic for more than 12 months. A separate data instrument was completed for these enrollees each year. During the time of yearly follow-up investigations from 1986 until the end of 1993, the clinic staff determined that 78 women had moved from Dakar and 53 women had no definitive information in their follow-up record. Eight seropositive enrollees and 3 seronegative comparison enrollees had died. After eight years of study, therefore, 77% of the original 574 enrollees were still available for follow-up or had expired. Furthermore, neither HIV-1 nor HIV-2 seropositive enrollees were significantly more likely to be lost to follow-up compared with seronegative enrollees in a logistic regression model controlling for nationality. As might be expected, being of non-Senegalese nationality was associated with missing a recent clinic visit.

In our study, AIDS as an outcome was defined according to the Centers for Disease Control (CDC) revised surveillance case definition for AIDS (27), and CDC IV HIV-related disease as an outcome was defined according to the CDC Classification System for HIV Infection (28). As shown in Table 4, incidence rates (IRs) for AIDS development or for CDC IV HIV-related disease development were strikingly different between HIV-2 seropositive women and HIV-1 seropositive women. Regardless of outcome, the rates for HIV-2 seropositive women, whether seroincident or seroprevalent, were consistently lower than those for HIV-1 seropositive women.

Incidence rate ratios for AIDS as an outcome comparing the IRs by serostatus were not meaningful because HIV-2 enrollees, the denominator in such a comparison, had no outcomes in the seroincident group after 112 PYO and only one outcome in the seroprevalent group despite 436 PYO. This comparison was possible, however, for CDC IV disease and for the development of abnormal CD4+ lymphocyte counts, defined as less than 400 cells/mm^3. Using a Cox proportional hazards model to compare seroincidence rates of

disease development in seroincident enrollees, HIV-1$_{IR}$ with HIV-2$_{IR}$, the hazard ratio was 6.31 [95% CI 1.23-32.24] for developing CDC IV disease and 12.14 [95% CI 1.41-104.39] for developing an abnormal CD4+ lymphocyte count.

Table 4. Incidence rates of disease development in enrollees according to HIV-1 and HIV-2 infection.

	HIV-1		HIV-2	
	Seroincident	Seroprevalent	Seroincident	Seroprevalent
Number of women	32	46	33	103
Total person years	82.50	106.50	111.91	436.17
Number of AIDS cases	4	1	0	1
AIDS incidence rate	4.85	0.94	0	0.23
95% CI	1.82-12.02]	[0.13-6.67]	—	[0.03-1.63]
Number of CDC IV cases	8	9	2	12
CDC IV incidence rate	9.70	8.45	1.79	2.75
95% CI	[4.85-19.39]	[4.40-16.24]	[0.45-7.15]	[1.56-4.86]

Using estimated seroconversion dates for seroincident enrollees, disease-free survival was analyzed via Kaplan-Meier product limit estimates (29). In this comparison, the likelihood of developing AIDS was significantly greater in the HIV-1 seroincident enrollees versus HIV-2 seroincident enrollees (Fig. 1; log rank test, p = .01 and Gehan's Wilcoxon test, p = .02). In seroincident HIV-1 infected women, the probability of AIDS-free time was 99% ± 1.0% at 2 years, 88.3% ± 7.8% at 3 years, 70.5% ± 13.4 at 4 years and 66.8% ± 14.3% at 5 years post infection. In contrast, no HIV-2 seroincident women developed AIDS, thereby exhibiting a 100% ± 0% probability of AIDS-free survival time greater than 5 years after infection. In addition, the likelihood of developing CDC IV disease as an outcome by disease-free survival analysis was significantly higher in the HIV-1 versus HIV-2 seroincident enrollees (Fig. 2; log rank test, p = .01 and Gehan's Wilcoxon test, p < .01).

The development of early immune compromise was further studied in seroincident enrollees. We noted the rate of occurrence of abnormal CD4+ lymphocyte counts (< 400 cells/mm^3) in seroincident enrollees and the development of skin test anergy in the subset of seroincident enrollees who agreed to multiple ppd tests and who were also initially positive to ppd skin testing. These analyses were independent of other disease outcomes. Assuming seroincident enrollees had similar CD4+ lymphocyte counts prior to infection with HIV-1 or HIV-2, this disease-free survival plot indicates that HIV-1 seroincident enrollees were significantly more likely to develop abnormal CD4+ counts over time than HIV-2 seroincident

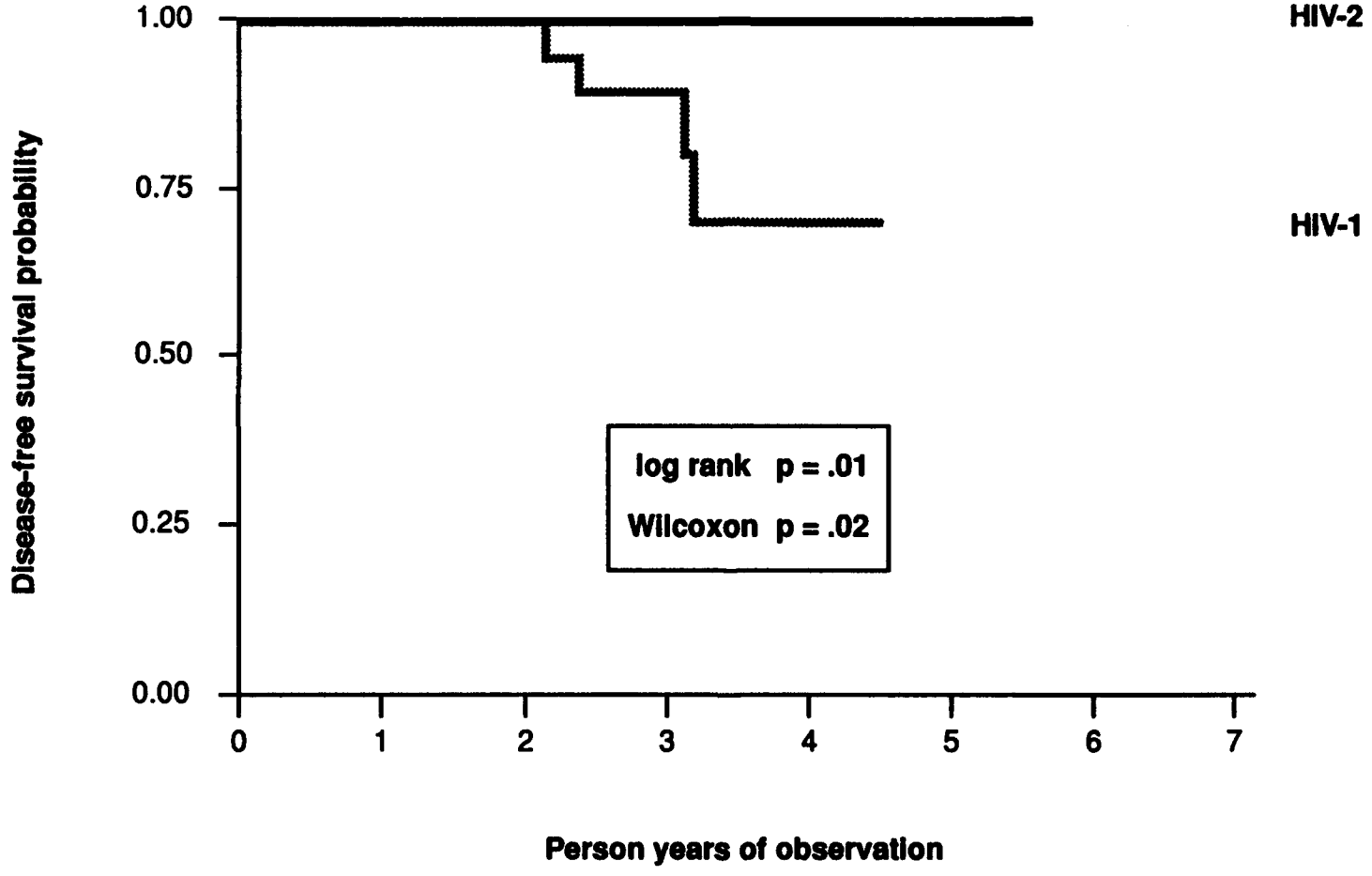
enrollees (Fig. 3; log rank test, $p < .01$ and Gehan's Wilcoxon test, $p < .01$). Furthermore, we looked at seroincident enrollees who were routinely skin tested over the period of the study and who had an initially positive ppd result. In those ppd skin test-positive seroincident women with multiple ppd skin test results, 6 of 17 HIV-1 seroincident women became anergic, whereas only 2 of 20 HIV-2 seroincident women became anergic over the study period (Fisher exact test, $p = .05$).

Most reports surveying the clinical manifestations of individuals infected with HIV-2 have previously been case-series or cross-sectional in nature (30-36). These types of studies are important in describing the epidemiological and clinical status of HIV-2 infected individuals. When controls are utilized, cross-sectional studies may also demonstrate disease association. In addition, two studies in West Africa obtained follow-up data on initially hospitalized AIDS patients seropositive for either HIV-1 or HIV-2 (35,36). When hospital-based surveys are used to identify index cases or subsequent cohorts of infected individuals, however, the apparent pathological effects of exposure to HIV-2 (or HIV-1) may not be fully appreciated or may be amplified by this type of case selection.

In general, disease association has been assessed by previous studies, but only prospective outpatient studies can assess the natural history and rate of disease development with asymptomatic HIV-2 infection. Our present investigation is the first formal report of a prospective, controlled clinical survey of initially asymptomatic HIV-2 seropositive individuals. Of note in the present survey is the comparison of the rate of immunologic compromise and clinical outcome of HIV-1 infection in the same setting and study population.

As shown in this population, the incidence rates for AIDS and HIV-related disease were distinctly lower for HIV-2 compared with that for HIV-1. Incidence rate ratios and disease-free survival analyses for AIDS and CDC IV disease between HIV-1 and HIV-2 demonstrate that the likelihood of developing disease with HIV-2 is significantly less than with HIV-1 infection. In fact, the rate of developing CDC IV disease may be several fold less for HIV-2 than HIV-1. Although study designs and methods of analyses have varied, the range of 65 to 80% AIDS-free survival with HIV-1 at 5 years is similar to our estimate of 67% at 5 years postinfection (37-39). The lack of AIDS cases seen in the HIV-2 seroincident enrollees observed for 112 person-years is noteworthy. Eventually, it will be possible to estimate the median survival time for HIV-2 infection in this setting.

Figure 1. AIDS disease-free survival in seroincident enrollees, according to serostatus.



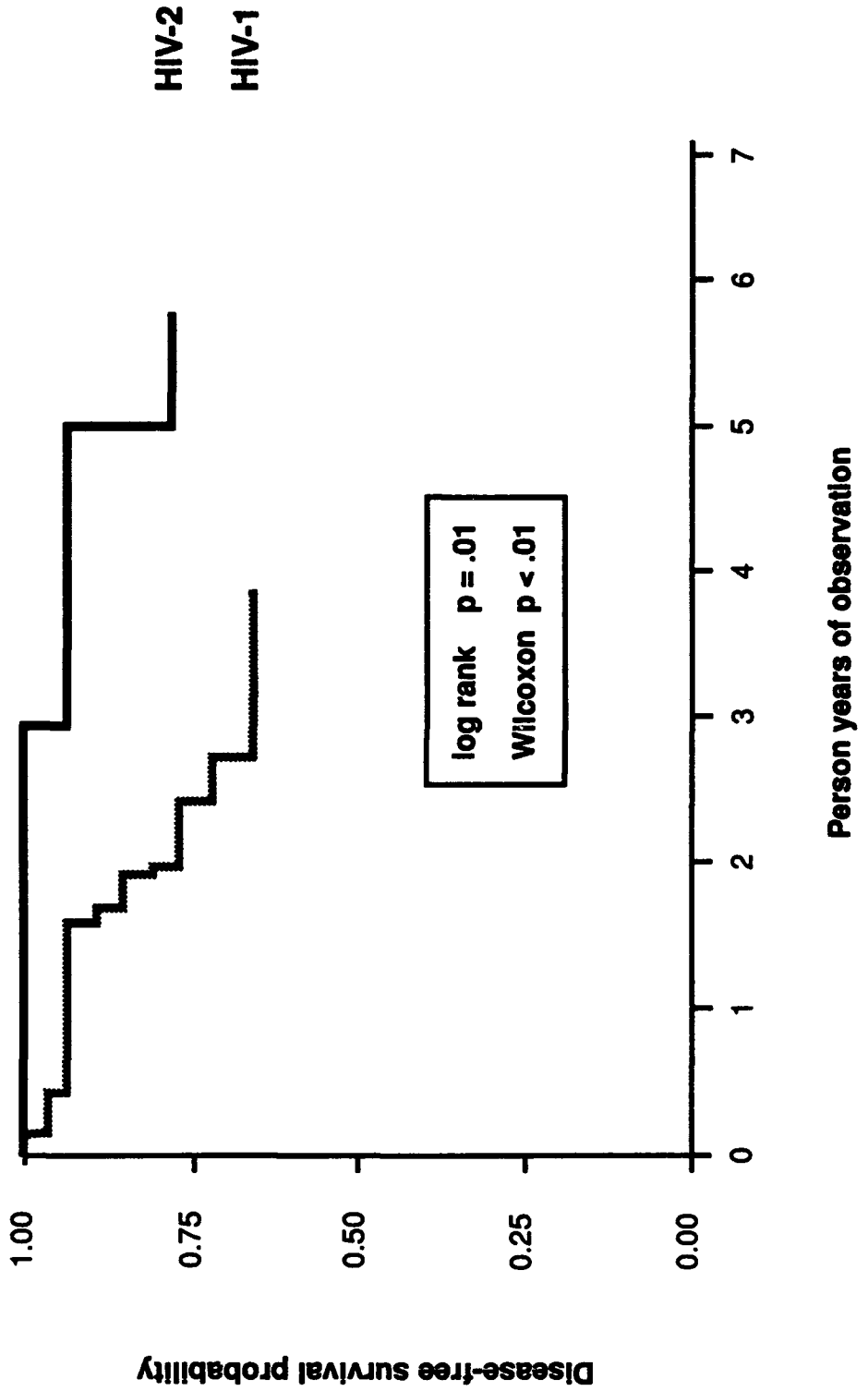


Figure 2. CDC IV disease-free survival in seroincident enrollees, according to serostatus.

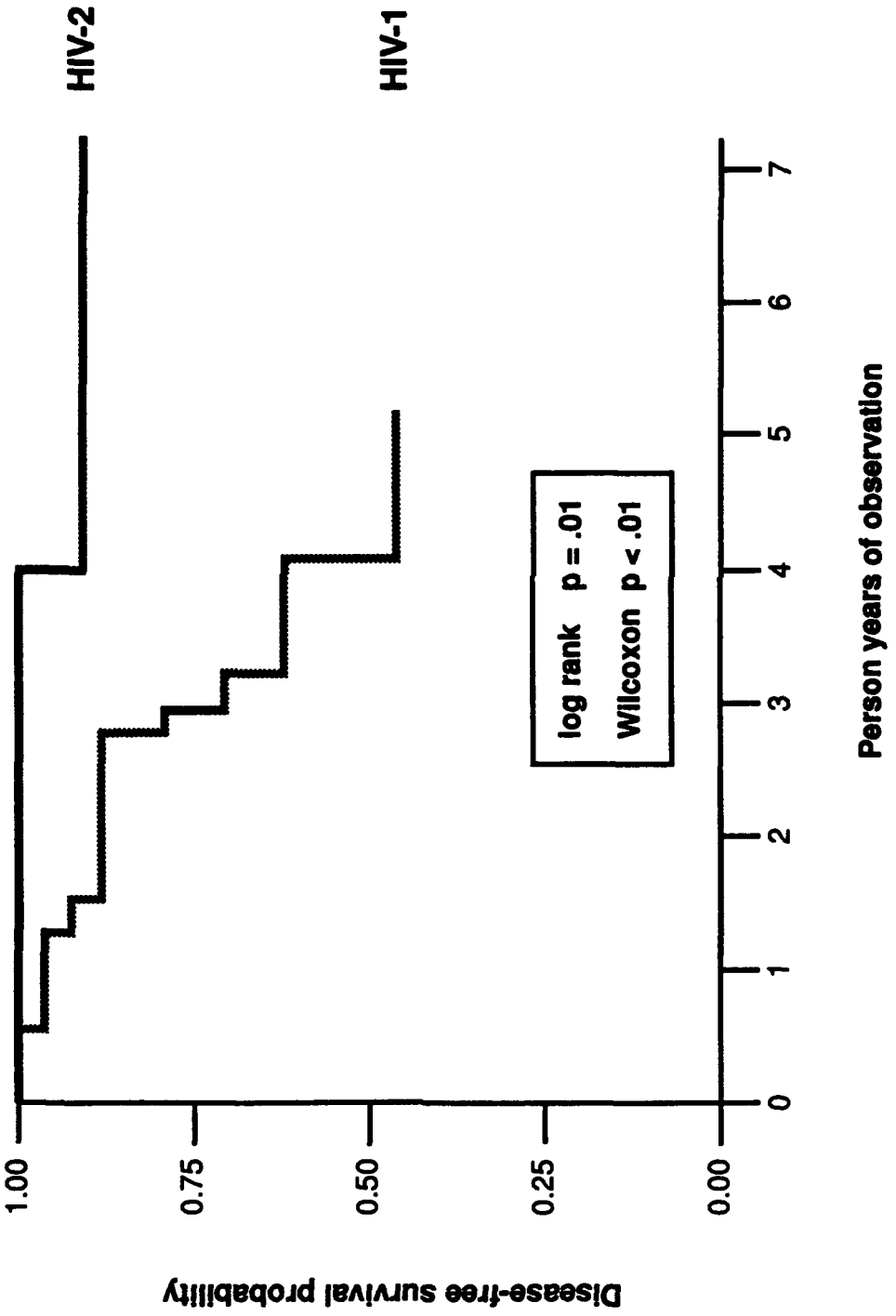


Figure 3. Disease-free survival as determined by CD4+ lymphocyte count in seroincident enrollees, according to serostatus.

This report further examines the intermediate immune alterations seen with HIV-2 infection compared with HIV-1 infection in an outpatient population (16,19) . These intermediate alterations were measured by T-cell subsetting and by delayed-type hypersensitivity skin testing. These analyses demonstrate that HIV-1 seropositives are more likely to develop low CD4+ lymphocyte counts during the early years following infection than HIV-2 seropositives. This reduced likelihood for immune compromise will be important in monitoring HIV-2 infected outpatients, in staging this human immunodeficiency virus infection, and perhaps in evaluating therapeutic decisions and responses.

Numerous studies have evaluated the rate of progression to AIDS in HIV-1 seropositive cohorts in North America and Europe. Recently, these studies have been complicated by the use of antiviral therapies. The rate of progression in African populations has been studied less frequently and none have described AIDS progression in seroincident cohorts (40,41). Moreover, until this report, the average observation period was not longer than 2 years. We feel that this clinical cohort will continue to document the distinct natural histories of HIV-2 versus HIV-1 infection. This population may also provide data on the rates of AIDS development in heterosexually acquired HIV-1 and HIV-2 infection, where antiviral therapy is not available.

HIV-1-related disease development was greater in seroincident enrollees than seroprevalent enrollees. Four of 5 HIV-1-related AIDS cases developed in the seroincident group. This most likely represents a selection bias via a "survivor effect" in those women enrolling in the seroprevalent group. Alternatively, it may also represent the movement of HIV-1 viral subtypes with more rapid disease outcome into the region, but this explanation remains to be investigated. Because of the range of rates of disease progression and the extreme rarity of outpatient natural history studies in an African setting, it is important to report cohort follow-up data for both the seroincident and seroprevalent enrollees. Overall, the presence of HIV-1 seropositive subjects as a comparison group in the same cohort in this study allowed for a more relevant examination of the rate of disease development of HIV-2 infection.

We have previously described distinct risk determinants for HIV-2 and HIV-1 infection in both prevalent and incident infection (17,18). Further, our analysis of HIV-2 and HIV-1 seroincidence strongly suggests differences in infectivity. Mathematical modeling of this data has suggested a 5-9 fold difference in the infectivity of HIV-2 compared with HIV-1 per sexual act (24). Perinatal transmission studies have also shown a 15-20 fold difference in the rate of HIV-2 transmission compared with HIV-1 transmission (42). In this study, we have shown that

HIV-2- and HIV-1-associated AIDS and CDC IV disease incidence rates are distinct, and the disease-free survival time for HIV-2 is significantly longer when compared with HIV-1. This study, therefore, supports the hypothesis that these two related HIV viruses have different biologic behaviors. One determinant of these differences may be a lower viral burden in HIV-2 infection, based on PCR and viral isolation studies (*see Objective 2)* . Whether this situation or other viral or host factors contribute to the reduced virulence of HIV-2 merits further investigation.

Studies concerning the natural history of infections or disease are difficult to achieve in any setting. Study bias can occur due to loss of participants. The high rate of follow-up in the present study was attained by a dedicated and energetic network of nurses, social workers and physicians. Individuals that were lost to follow-up were not more likely to be HIV seropositive for either HIV-1 or HIV-2. Estimates of disease outcome, therefore, did not seem to be biased towards infection with one virus or another. We hope that this population will continue to document the natural histories of both HIV-2 and HIV-1 infection in West Africa. In addition to prospective data for modeling of the HIV-2 and HIV-1 epidemics in West Africa, such follow-up studies may provide prognostic information for HIV-2 seropositive persons. Moreover, further investigations into basic differences in biology, which may explain the distinct rates of disease development with HIV-1 versus HIV-2, should be encouraged by these findings.

OBJECTIVE 2:

Characterization of the Immune response and Viral Carriage of HIV-2.

The understanding of the differences in the epidemiology and natural history of HIV-2 infection compared to HIV-1, leads to obvious questions regarding differences in the immune response to these viruses. The basic premise would be that virus-host immune response interactions would be responsible for differences in longer clinical incubation periods, transmission and overall pathogenesis. Studies conducted under the previous contract, indicated similarlity in gross quantitative and qualitative humoral immune response to HIV-2 antigens. These studies have looked at other accessory gene products of HIV-2 as well as epitopes of the envelope antigen.

Our main objective in these studies was to evaluate the utility of various serologic markers for use in distinquishing HIV-1 from HIV-2 infection. In addition, we wished to assess

differences in humoral immune response to certain viral antigens that might provide useful data for disease prognosis. These included recombinant expressed env peptides from HIV-1 and HIV-2, and recombinant-expressed vpx and vpu proteins the unique gene products of HIV-2 and HIV-1, respectively.

Evaluation of HIV recombinant-env peptides

(Cost-Effective Diagnosis of HIV-1 and HIV-2 By Recombinant-Expressed env Peptide (566/966) Dot Blot Analysis. AIDS 7:481-95 (1993). (43)).

Serum samples were obtained from West African individuals previously serodiagnosed by whole viral lysate immunoblots to HIV-1 (IIIb) and multiple HIV-2 isolates (MS-U937, NIH-Z and ST). Semi-purified recombinant-expressed HIV-1 (566) and HIV-2 (996) env proteins, homologous with the N-terminal region of gp41 (HIV-1) and gp35 (HIV-2), have been described (44,45). These antigens were evaluated in an immunoblot assay and then adapted to a dot-blot miniblotter technique as described in the published manuscript (43).

Table 5: Antibody Reactivity to Recombinant *env* peptides (566/996)

	HIV-1 566	HIV-2 996
HIV-1 Seropositive Central & West Africa USA and Mexico	77/77 (100%)	44/77 (57%)
HIV-2 Seropositive Senegal	0/28 (0%)	28/28 (100%)
Guinea Bissau	0/12 (0%)	12/12 (100%)
HIV Dual Reactive	37/37 (100%)	37/37 (100%)
HIV Negative Central & West Africa USA and Mexico	0/17 (0%)	0/17 (0%)

The HIV-2 seropositive samples detected the HIV-2 recombinant env peptide (996) 100%(40/40) of the time with 0% (0/40) cross-reactivity to the HIV-1 peptide (566) (table 5). HIV-1 seropositive samples from 4 diverse geographic origins demonstrated 100% reactivity (77/77) to the HIV-1 specific peptide (566) with substantial cross-reactivity 57% (44/77) to 996. Dual-reactive sera detected both recombinant peptides 100% (37/37). None of the HIV negative sera reacted nonspecifically to these envelope peptides.

The 556 HIV-1 env peptide was found to be type-specific, whereas the 996 HIV-2 peptide demonstrated significant cross-reactivity. In summary, the 566 (HIV-1) peptide showed 100% sensitivity and specificity. The 996 (HIV-2) peptide performed similarly, but showed the presence of HIV-1 cross-reactive epitopes (Table 5). When the two env peptides were used together, there was high specificity and sensitivity for detecting HIV positive sera both in immunoblot and dot blot formats. Of note, all 55 immunoblot defined HIV- Dual reactive sera had strong antibody responses to both the 556 (HIV-1) and 996(HIV-2) recombinant env peptides. The dot blot assay performed in the field on over 2700 samples, showed slightly lower specificity and sensitivity for HIV diagnosis. The relative cost of this assay was 10-fold lower than conventional commercial assays and could be easily performed in less than 2 hours.

Evaluation of vpx and vpu reactivity for HIV diagnosis

Recombinant-expressed vpu (HIV-1) (46) and vpx (HIV-2) (47) have been described and are immunogenic in some proportion of infected individuals. Since these are unique gene products of the different HIVs, positive anti-vpx and anti-vpu reactivity established proof of at least one round of active viral replication for both viruses and therefore suggestive of dual infection. Serum samples were obtained from West African individuals previously serodiagnosed by whole viral lysate immunoblots to HIV-1 (IIIb) and multiple HIV-2 isolates (MS-U937, NIH-Z and ST). Semi-purified recombinant-expressed HIV-1 (566) and HIV-2 (966) env proteins, homologous with the N-terminal region of gp41 (44) and gp35 (45), have been described. All recombinant expressed proteins were analyzed by immunoblot.

Reactivity of HIV-2 positive samples on recombinant expressed vpx was low with 8.4% (19/227) reactivity and no reactivity to vpu (0/227), 65 HIV negatives were vpx negative (Table 6). Dual reactive sera showed a comparable rate of reactivity to vpx and vpu as single virus infected individuals. Thus, in some instances vpx and/or vpu was useful in diagnosing HIV-Dual status.

Table 6: Antibody Reactivity to Recombinant HIV-1 *vpu* and HIV-2 *vpx*

	HIV-1 *vpu*	HIV-2 *vpx*
HIV-1 Seropositive Central & West Africa and Mexico	34/81 (42%)	0/81 (0%)
HIV-2 Seropositive	0/227 (0%)	19/227 (8.3%)
HIV Dual Reactive West Africa	44/112 (39%)	11/112 (10%)
HIV Negative Central & West Africa and Mexico	0/65 (0%)	0/65 (0%)

By using a panel of serologic assays including: immunoblot, RIP-SDS/PAGE, recombinant -env peptides and vpx/vpu testing we have found 0.7% Dual reactivity in our cohort of 1354 registered prostitutes. Given an HIV-1 prevalence of 4.7% and an HIV-2 prevalence of 10.8% ,we would predict 0.51% dual reactivity if the the viruses were behaving independently. This is not the general experience of other studies in the literature where the observed versus expected prevalence of dual reactivity has ranged from 7-15 (7,48-50). Although the existence of an intermediate virus in these other populations, cannot be dismissed, it is apparent that the reported discrepancy between observed and expected values has dropped dramatically as the techniques for distinguishing the two viruses has improved. Therefore, it seems likely that the discrepancy between the expected and observed values for dual reactivity is due to extensive serologic crossreactivity. The group of individuals infected with both viruses, as confirmed by PCR, is also predicted by the prevalence of each virus type (49,50).

HTLVs in Senegal

In addition to our assessment of the biology of HIV viruses in Senegal, we have concurrentl evaluated the presence of HTLV viruses as well. Sera from 1021 individuals and 8 periphera

blood lymphocytes (PBL) DNA were obtained from female prostitutes from our cohort study ir Dakar and Ziguinchor, Senegal. Immunoblot was performed using HUT-102 cell lysate as antigen on all sera, RIPA was used for confirmation. Sera from 103 individuals (10%) met the criteria of HTLV positivity (reactivity to 2 viral bands) and 16 (1.6%) were indeterminate (reactive with 1 viral band). All indeterminate samples were further evaluated by RIPA .

All blot positive sera and indeterminate sera were analyzed on recombinant-expressed HTLV-I (B-I) and HTLV-II (II-B) envelope proteins (51) by immunoblot. Among the 103 HTLV positive individuals 71 (69%) had antibodies against B-I, suggesting an HTLV-I infection, and 5 against II-B only. One sample showed strong reactivity suggestive of HTLV-2 infection, PBL DNA was not available. None of the blot indeterminate samples showed reactivity to the HTLV recombinant env proteins.

HIV-2 Cytotoxic Lymphocyte (CTL) Response

In collaboration with Bruce Walker at Mass General Hospital we have been studying the generation the cytotoxic lymphocytes directed to HIV-2 (52). Target cells for these assays consisted of autologous EBV lymphoblasts infected with recombinant vaccina virus expressed the HIV-2 ROD and ST env genes, the SIV251 env gene, SIV gag gene, HIV-2 RT gene and a control vaccina virus. Effector cells consisted of: 1)Fresh unstimulated PBMCs; 2) CD8+ enriched lymphocytes, which had been expanded in vitro with interleukin2; and 3) PBMCs cloned at limiting dilution using a CD3-specific monoclonal antibody as a stimulus to T cell proliferation.

HIV-2 env-specific CTL activity was detected in 4/6 seropositive subjects. In 3/4, no env-specific activity was detected in fresh PBMCs or expanded CD8+ cells, although clones were obtained from these individuals which recognized SIV251env. In 1/4, ST-specific activity was detected in the expanded CD8+ lymphocytes, although no clone could be isolated from this subject. In 1/6 subjects, there was marked gag-specific CTL activity, which could be detected using target cells expressing the SIV gag protein. Two epitopes within gag were mapped using synthetic viral peptides. The HLA-restriction of these epitopes is under investigation. RT-specific activity was not detected in any subject, and in 2/6 subjects there was no detectable CTL against any gene using these methodologies.

Quantitative PCR for HIV-2 and HIV-1

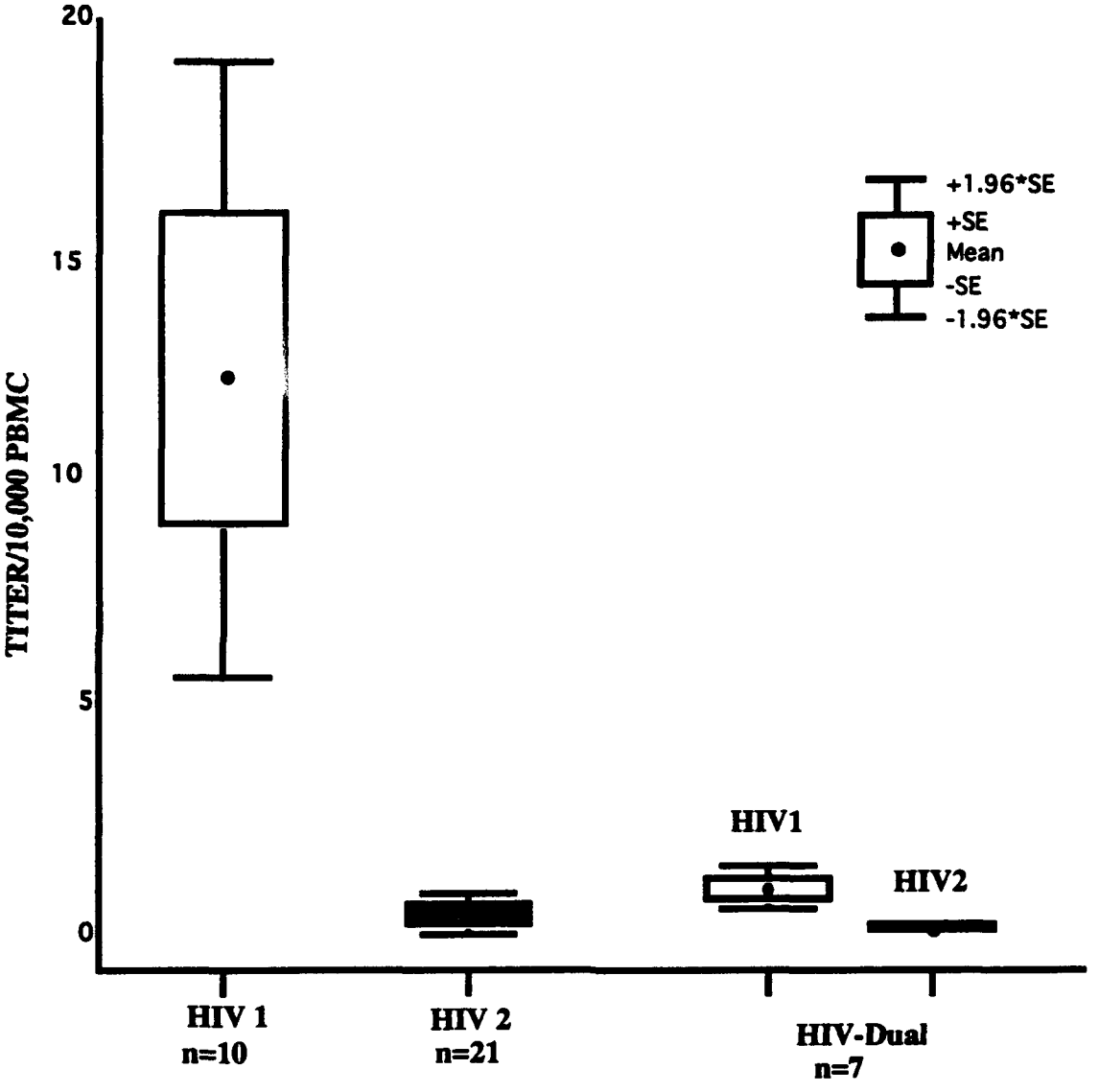
Viral burden is a virologic determinant that is considered to play a role in HIV pathogenesis, we have recently developed quantitative DNA PCR techniques for both HIV-1 and HIV-2.

We hypothesize that the differences in transmission and incubation to disease between the two HIVs may be due in part to a lower viral burden in HIV-2 compared to HIV-1. We have used nested primers for HIV-1 (53) and HIV-2 (54). The ^{32}P-labeled inner primer pair therefore produces a radiolabeled amplified product which can be verified for size in the 2% agarose gel by ethidium bromide staining and the band cut out and counted in a scintillation counter (55). Quantitation of viral copy for HIV-1 was obtained by comparing cpm of PBMC DNA samples to a standard curve generated by serial dilution of 8E5 cells, known to contain one proviral copy of HIV-1 per cell (56). Quantitation of HIV-2 proviral copy was determined using a standard curve generated by serial dilution of HIV-2 plasmid JSPH27 (57) diluted in negative PBMC DNA. All PBMC DNA samples were independently evaluated for the quality of DNA by separate betaglobin PCR (55). For each assay run, standard curves were generated with negative PBMC DNA and no DNA (blank) controls. Proviral titers were expressed as viral copies per 10,000 PBMC.

The HIV-1 gag primers were evaluated for specificity on 3 HIV-1 cell culture DNAs. In addition, 2 HIV-2 PBMC DNA samples, 3 HIV-1 cell culture DNAs and 5 seronegative DNAs and found to be HIV-1 specific. Based on the dilution curve of 8E5 cells, the PCR reaction was capable of detecting 10 HIV-1 copies. Of 12 HIV-1 PBMC DNA samples from HIV-1 antibody samples, 10 were found to be PCR positive (83.3%); with a mean proviral titer of 12.35 copies per 10,000 PBMCs with a range of 1.85 to 37.39/10,000 PBMC; which is consistent with HIV-1 proviral titers reported by others (53,58). (Figure 4)

The HIV-2 gag primers were evaluated for specificity on 3 HIV-2 cell culture DNAs and found to be positive. In addition, 6 HIV-1 PBMC DNA samples, 4 HIV-1 cell culture DNAs and 10 seronegative DNAs were PCR negative. Based on the plasmid standard curve, PCR was found to detect 1 proviral copy. In 22 PBMC DNA samples from HIV-2 antibody samples, 21 (95.4%) were found to be PCR positive. with a mean proviral titer of 0.37/10,000 PBMC with a range of 0.02-5/ 10,000 PBMC (Figure 4). Given these data, we believe that HIV-1 proviral titers are approximately 33 fold higher than HIV-2 proviral titers. This suggests that low HIV-2 viral burden may play a role in the differences in biology of HIV-2 as compared to HIV-1. Although the data is still preliminary, we believe that this technique will be useful to evaluate the role of viral burden in HIV pathogenesis and in understanding the interactions of HIV-2 and HIV-1 in vivo as proposed in the new studies.

Figure 1 : Mean Proviral Titers of HIV-1, HIV-2 and HIV-Dual



Preliminary studies on HIV-Dual Reactive Individuals

Since 1986, a number of West African countries have reported significant rates of individuals with a HIV- Dual serologic profile (2,15,42). This antibody profile is characterized by antibodies with equally strong reactivity to the env antigens of both HIV-1 and HIV-2 by immunoblot and/or RIP-SDS/PAGE, since significant cross-reactivity is known to exist in the major gag and pol antigens. Using these criteria as gold standards, a number of

recombinant or synthetic peptide based envelope antigens have been described as HIV-type specific (43-45). A number of explanations for this type of serologic HIV-dual reactivity must be entertained including: extensive cross-reactivity by either of the HIVs, dual infection, infection by one type and exposure to a second type, or infection with an intermediate virus.

Isolation of both HIV-1 and HIV-2 has been reported from one such HIV- dual individual from Ivory Coast (59); and PCR evidence of HIV-1 and HIV-2 infection has been reported in similar populations (60). Two studies have recently been reported from the Ivory Coast, where one study showed 21/34 (61.7%) serologically diagnosed HIV-duals were confirmed by PCR (49), whereas a second report demonstrated 12/36 (33.3%) (50). Differences in the serologic diagnosis of HIV-Duals and the sensitivity and specificity of the PCR primers may be responsible for these different results. Nonetheless, it is clear that significant Dual infection as measured by DNA PCR does occur in populations with significant prevalence rates of both virus types. The clinical significance of Dual infection is yet to be determined and represents an important area for further study.

CONCLUSIONS

In addition to prospective data for modeling of the HIV-2 and HIV-1 epidemics in West Africa, follow-up studies such as this one may provide prognostic information for the thousands of HIV-2 seropositive persons. Also, further investigations into basic differences in biology or pathogenesis of HIV-1 versus HIV-2 should be encouraged by these findings. One should not minimize, however, the potential consequences of HIV-2 infection by this data. Only after further studies are completed concerning the transmission rates of HIV-2, the natural history of the diseases associated with HIV-2 and the follow-up of seroincident cohorts, can the full impact of this immunodeficiency virus be appreciated.

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EPIDEMIOLOGY AND TRANSMISSION OF HIV-2 IN SENEGAL Kanki P., Mboup S, Marlink R, Siby T, Travers K., Essex M; Harvard School of Public Health, Boston,MA, USA; University of Dakar, Dakar Senegal

EMERGENCE OF HIV-1 IN A HIGH RISK GROUP FROM AN HIV-2 ENDEMIC AREA (SENEGAL) Mboup S, Kanki P., Ndoye I, Siby T, Sankalé JL, Gueye A, Boye C, Marlink R, Essex M; University of Dakar, Dakar, Senegal; Harvard School of Public Health, Boston, MA, USA.

Vth International AIDS in Africa Conference-Kinshasa, Zaire October 1990

REPORT DES PREMIERS CAS CLINIQUES AU DEIN D'UNE COHORTE DE SEROPOSITIFS HIV-2 ET HIV-1 AU SENEGAL Thior Ibou, Siby T, Marlink R, Gueye A, Sankalé JL, Ndoye I, Kanki P., Essex Mboup S; Bacterio-Virologie, Faculté de Médecine et Pharmacie, Université Cheikh Anta Diop, Dakar, Senegal; Cancer Biology, Harvard School of Public Health, Boston, MA, USA; Service MST, Institute d'Hygiene Sociale, Dakar.

CO-INFECTIONS HIV-2 ET HTLV-1 AU SENEGAL Sankalé JL, Gaye A, Dia M, Gueye EH, Verdier M, Denis F, Mboup S, Essex M, Kanki P.; Department of Cancer Biology, Harvard School of Public Health, Boston; Bacterio-Virologie, Faculté de Médecine et Pharmacie, Université Cheikh Anta Diop, Dakar, Senegal; Virologie, CHU Dupuytren, Limoges, France.

ANALYSIS OF HIV-SPECIFIC IMMUNE COMPLEXES AND HIV ANTIGEN IN HIV-INFECTED ZAIRIANS Kashala LO, Diese M, Mukeba Prudence, Kanki P., Kayembe K, Kalengayi M, Essex M; Department of Cancer Biology, Harvard School of Public Health, Boston, MA, USA, Department of Internal Medicine, University of Kinshasa, Kinshasa, Zaire, Department of Pathology, University of Kinshasa, Zaire.

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PROSPECTIVE STUDY OF THE NATURAL HISTORY OF HIV-2 Marlink R, Thior, I, Dia Mamadou Ciré, Gueye, E.H., Ndoye, I, Essex, M, Mboup, S, Kanki, P; Harvard School of Public Health, Boston, MA, USA, University of Dakar, Dakar, Senegal

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CLINICAL TESTING OF NEW TYPE-SPECIFIC ANTIGENIC DOMAIN IN THE HIV-2 ENVELOPE Huang M, Kanki P, Essex M; Harvard School of Public Health, Boston, MA, USA

PROGNOSTIC VALUE OF HIV ANTIGEN, P24 RELATIVE BINDING CAPACITY AND HIV-SPECIFIC IMMUNE COMPLEX (CIC) Kashala L, Diese M, Mukeba P, Kanki P., Kayembe K, Kalengyi M, Essex M

SERODIAGNOSIS OF HIV BY RECOMBINANT ENV AND VPX/VPU PEPTIDES Gueye A, Kanki P., Samuel K, Mboup S, Marlink R, Papas T, Essex M; Harvard School of Public Health, Boston, MA , USA; NCI-FCRDC, Frederick, MD, USA; University of Dakar, Dakar, Senegal

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HISTOIRE NATURELLE DE L'INFECTION HIV2 A ZIGUINCHOR, SENEGAL Dia MC, Sall, I; Mane, I Sankale, JL; Siby, T; Marlink, R; Travers, K; Mboup, S, Essex, M; Kanki P; Bacteriologie-Virologie, Faculte de Medecine et Pharmacie, Universite C.A. Diop, Dakar, Senegal; Hopital Regional de Ziguinchor, Ziguinchor, Senegal; Region medicale de Ziguinchor, Ziguinchor, Senegal; Department of Cancer Biology, Harvard School of Public Health, Boston, MA, USA

PREVALENCE DU VIH ET MST MAJEURES CHEZ LES PROSTITUTEES NOUVELLEMENT INSCRITES Diaw I; Thior, I; Siby T; Ndaw, M; Dabo, L; Mbengue, M.D.; Ndoye, I; Mboup, S; Universite Cheikh Anta Diop; Bureau National des MST-IHS

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QUANTITATION OF HIV-2 VIRAL LOAD IN CLINICAL SAMPLES USING LABELED PRIMER POLYMERASE CHAIN REACTION. D Hamel, P. Kanki, R. Marlink, T. Siby†, S. Mboup, K. Travers, et. al. Department of Cancer Biology, Harvard School of Public Health, Boston, MA., †Laboratoire de Bacteriologie-Virologie, Hôpital A. Le Dantec, Dakar, Sénégal

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