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Natural Protection Against HIV-1 Infection Provided by HIV-2

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tropins (14). Although TIMP-1 binds to interstitial collagenase with high (subnanomolar) affinity (15), the metalloproteinase-inhibiting activity is apparent only at TIMP-1 concentrations of 1 to 3  $\mu\text{g/ml}$  (7). STP activity of the 28-kD (TIMP-1)–38-kD (procathepsin L) complex is apparent at concentrations of 30 to 100 ng/ml. TIMP-1 was originally described as an erythroid potentiating factor (16) and exhibits growth factor activity at concentrations of 30 to 100 ng/ml (17). Thus, TIMP-1 appears to be a multifunctional protein with tissue-specific activities.

Cathepsin L is a lysosomal cysteine protease that is present in many tissues and functions in the metabolism and turnover of intracellular proteins (8). It is synthesized as a proenzyme (39 kD), which is processed and targeted to lysosomes by the mannose-6-phosphate receptor (8). Procathepsin L is the major protein released by malignantly transformed mouse fibroblasts (8). Cathepsin L cleaves various intracellular and extracellular proteins, including serum proteins and components of the extracellular matrix (8), and has been implicated in biological processes such as tumor invasion and metastasis, bone resorption, pro-hormone activation, and sperm maturation (8, 9). Procathepsin L is also identical to CP-2, a Sertoli cell product secreted by the seminiferous tubules during a specific period of spermatogenesis; maximal synthesis and secretion occur at the time of initiation of meiosis and spermatid release (9). Medium from cultured seminiferous tubules at this specific stage shows the greatest stimulatory effect on androgen production by Leydig cells (18). Thus, it appears that STP secretion in the adult is under the control of specific germ cell types (3). The precise role of procathepsin L in STP is not clear. Because TIMP-1 has 12 conserved cysteine residues paired into six disulfide bonds, cleavage of these bonds by a cysteine protease might contribute to the expression of maximal STP bioactivity.

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Significant differences have been observed in the rates of transmission and disease development in human immunodeficiency virus (HIV) types 1 and 2. Because many HIV-2-infected people remain asymptomatic for prolonged periods, the hypothesis that HIV-2 might protect against subsequent infection by HIV-1 was considered. During a 9-year period in Dakar, Senegal, the seroincidence of both HIV types was measured in a cohort of commercial sex workers. Despite a higher incidence of other sexually transmitted diseases (STDs), HIV-2-infected women had a lower incidence of HIV-1 than did HIV-seronegative women, with a relative risk of 0.32 ( $P = 0.008$ ). An understanding of the cross-protective mechanisms involved may be directly relevant to HIV-1 vaccine development.

HIV-1 and HIV-2 share substantial genetic relatedness, partial antigenic cross-reactivity, and a common cellular receptor. Although HIV-1, the prototype acquired immunodeficiency syndrome (AIDS) virus, has reached epidemic proportions throughout the world, HIV-2 is largely confined to West Africa, where varying rates of HIV-1 infection have been reported (1). Studies

conducted in West Africa have shown that although both viruses are transmitted by similar routes, the rates of sexual and perinatal transmission of HIV-2 are significantly lower than those of HIV-1 in the same populations (2–4). Initial cross-sectional reports of HIV-2 suggested an association of HIV-2 infection with AIDS (5) that appeared to be weaker than the association of

HIV-1 infection with AIDS (6). More recently, in a 9-year prospective study in Dakar, Senegal, we showed that the disease-free survival time for HIV-2 was significantly longer than for HIV-1 (7). Thus, the current data suggest that despite a number of shared virologic characteristics, HIV-1 and HIV-2 have distinct biologic properties. Few data are available on the interaction of these two viruses at the host or population level.

In West African populations at risk for both HIV-1 and HIV-2, some individuals have been described who exhibit antibody reactivity to the type-specific *env*-encoded antigens of both HIV-1 and HIV-2 (8). In recent years, more discriminating serologic assays and the availability of the polymerase chain reaction (PCR) have allowed researchers to better characterize individuals with dual reactivity. Possible explanations for this HIV dual reactivity include extensive cross-reactivity by either virus, infection with both viruses, or infection with an intermediate virus. Isolation of both HIV-1 and HIV-2 has been reported from one such individual with dual reactivity, and PCR evidence of both viruses has been reported in selected individuals (9). However, little progress has been made in the epidemiologic characterization of this apparent virus interaction.

Our previous observations from a cohort of commercial sex workers in Senegal have demonstrated a stable HIV-2 incidence rate (IR) of approximately 1.0 per 100 person-years of observation (PYO) over the 9-year study period (3). In contrast, HIV-1 infection has spread rapidly, with the HIV-1 IR at the end of the study period being 12 times that at the start. Over time, we have observed HIV-2-infected women and measured the occurrence of subsequent HIV-1 infection. Thus, with this cohort, we could directly test the hypothesis that susceptibility to HIV-1 could be altered in individuals already infected with the antigenically related but less virulent HIV-2.

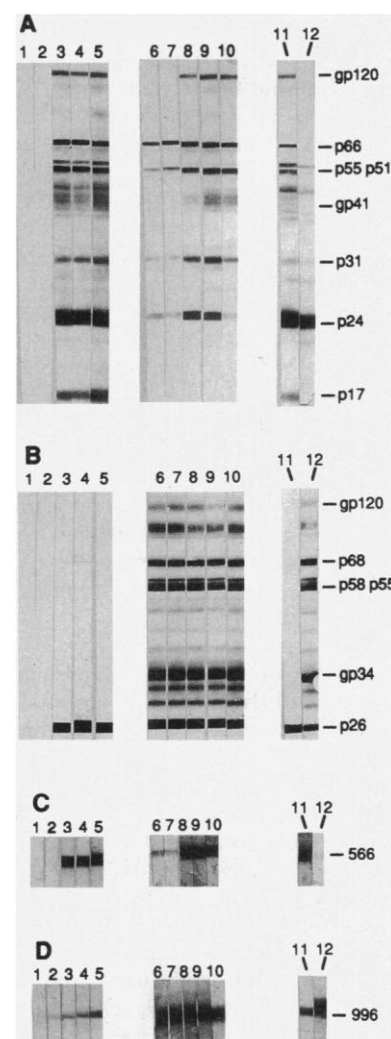
From 1985 to 1994, registered commercial sex workers who had given informed consent at the Institut d'Hygiène Sociale clinic in Dakar were clinically followed, with sequential serum samples obtained at each visit; the study design has been described (2, 3, 7). These serum samples were evaluated by immunoblot for antibody re-

activity to the major viral antigens of HIV-2 and HIV-1 (Cambridge Biotech, Worcester, Massachusetts). The samples were classified as seropositive to either virus antibodies reactive to *env* in the presence or absence of *gag*, or *pol* antigens were detected. To avoid misclassification, we confirmed results that indicated seroconversion by retesting the serum sample along with the same individual's previous serum samples. All serum samples showing dual reactivity were retested with the sensitive and specific recombinant peptides from the envelope regions of HIV-1 and HIV-2, designated 566 and 996, respectively (10).

Dual infection was confirmed by PCR evidence of both viruses in DNA samples from peripheral blood mononuclear cells (PBMCs) (11). Women attending the clinic were regularly evaluated for STDs. Routine serologic evaluation for incident syphilis infection was performed with Rapid Plasma Reagin (RPR; BBL Microbiology Systems, Cockeysville, Maryland) followed by *Treponema pallidum* Haemagglutination Assay confirmation (TPHA; Miles Diagnostics, Elkhart, Indiana). At each clinical visit, swabs were obtained for culture of *Neisseria gonorrhoeae*. The STDs were considered independent new infections if two sequential positive results were at least 6 months apart.

The cohort for the present study included women who had been identified as seropositive for HIV-1 or HIV-2; for follow-up equivalence, each seropositive woman was matched to two randomly selected women who were seronegative for both HIV-1 and HIV-2 on the basis of age ( $\pm 2$  years), nationality, and number of years of registered prostitution ( $\pm 3$  years) (7). A total of 756 women were enrolled and prospectively followed over the course of the study period. Of this group, 138 women were HIV-2-seropositive on entry, and the remaining 618 women were HIV-seronegative. Forty-nine women from the initially seronegative group converted to HIV-2 seropositivity; the lengths of observation time before and after their estimated dates of HIV-2 seroconversion were evaluated as HIV-2-seronegative and HIV-2-seropositive person-time, respectively. All eligible women were asked to participate in the study, and all gave their informed consent before enrollment. Clinical assessment and routine CD4/CD8 determinations were conducted (7). Because seroprevalent HIV-1 cases were infected before serologic evaluation, they were excluded from the analysis of HIV-1 IRs. Over the study period, two HIV-seronegative women appeared to seroconvert to both HIV-1 and HIV-2 simultaneously; the estimated seroconversion date for each woman was the same for both HIV types. These women were excluded from the analysis (12).

Typical sequential serologic profiles of HIV-1 seroconversion in an initially HIV-seronegative individual are shown (Fig. 1A, lanes 1 to 5). Seroconversion to all of the major antigens of HIV-1 on whole-virus immunoblots was demonstrated with concurrent cross-reactivity to the HIV-2 *gag*-encoded antigen p26 (Fig. 1B, lanes 3 to 5). This seroconversion was confirmed by strong reactivity to the HIV-1-specific peptide 566 (Fig. 1C, lanes 3 to 5), with limited cross-reactivity to the HIV-2-specific peptide 996 (Fig. 1D, lanes 3 to 5). HIV-1 seroconversion in an initially HIV-2-seropositive individual was demonstrated by the



**Fig. 1.** Representative sequential serologic profiles of HIV-negative seroconversion to HIV-1 (lanes 1 to 5) and of an HIV-2-infected woman who seroconverted to HIV dual reactivity (lanes 6 to 10). Lane 11, reference HIV-1-positive control; lane 12, reference HIV-2-positive control. The immunoblots show reactivity to (A) HIV-1 viral antigens encoded by *env* (gp120, gp41), *pol* (p66, p55, p31), and *gag* (p55, p24, p17); (B) HIV-2 viral antigens encoded by *env* (gp120, gp34), *pol* (p68, p58), and *gag* (p55, p26); (C) HIV-1 recombinant *env* peptide (566); and (D) HIV-2 recombinant *env* peptide (996).

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appearance of the specific response to the HIV-1 antigens gp41 and gp120 (Fig. 1A, lanes 8 to 10), whereas reactivity to all of the HIV-2 major antigens was demonstrated in all bleeds (Fig. 1B, lanes 6 to 10). Reactivity to peptide 566 (Fig. 1C, lanes 8 to 10) confirmed HIV-1 seroconversion in the presence of a strong and persistent response to peptide 996 (Fig. 1D, lanes 6 to 10).

Over the study period, the IRs of HIV-1 infection in HIV-seronegative and HIV-2-seropositive women were measured annually (Table 1). Of the 618 women who were initially HIV-seronegative, 61 seroconverted to HIV-1; the overall HIV-1 IR in this group was 2.53 per 100 PYO (Table 1). Among the 187 women who were initially HIV-2-seropositive or who seroconverted to HIV-2 during the study period, 7 seroconverted to an HIV dual-reactive status. All seven women were PCR-positive for both viruses in PBMC DNA, and all demonstrated seroconversion to both recombinant type-specific proteins. The overall HIV-1 IR in the HIV-2-seropositive group was 1.06 per 100 PYO (Table 1), which was lower than the IR among the HIV-seronegative group. No incident HIV-1 infections were noted before 1987; a trend of increasing HIV-1 IR over calendar time was observed in both groups.

Confounding could have been present in the data if the HIV-2-seropositive women adopted safer sex practices after learning their HIV serostatus and receiving counseling. To address the comparability of baseline HIV-1 exposure in the HIV-2-seropositive and HIV-seronegative groups, we evaluated STDs as objective surrogate markers for high-risk sexual behavior. Several reports have suggested that gonorrheal infection is significantly associated with HIV-1 seroconversion as a marker of sexual behavior (13), which we considered more reliable than self-reported sexual behavior data. Although univariate analysis showed a significantly lower HIV-1 IR among the HIV-2-seropositive women than among the initially HIV-seronegative women, with a relative risk (RR) of 0.43, the IR of gonorrhea in this HIV-2-seropositive group was significantly higher (RR = 1.51) (Table 2). The IR of syphilis was also higher in the HIV-2-seropositive group, although it was not statistically significant (RR = 1.40) (Table 2).

We next constructed a multivariate Poisson regression model (14). This model supported previous observations that calendar year was a significant predictor of HIV-1 seroconversion (3), with an adjusted RR of 1.25 ( $P = 0.02$ ) associated with each additional year of exposure (Table 3). The model also indicated an association between HIV-2 seropositivity and decreased risk of HIV-1 infection, with an adjusted

RR of 0.32 ( $P = 0.008$ ). This finding supported the results of the univariate analysis (Table 2). There was little difference between multivariate models that included and omitted syphilis infection (15), and this variable was dropped from the final model.

Because univariate analysis indicated that HIV-2-seropositive women with CD4<sup>+</sup> cell counts less than 800 per cubic millimeter were more likely to become infected with HIV-1 than were those with higher CD4<sup>+</sup> cell counts (Fisher exact test,  $P < 0.03$ ), we constructed a model as above, with the additional variable of CD4<sup>+</sup> cell count. CD4<sup>+</sup> cell counts less than 800 per cubic millimeter were signifi-

cantly predictive of HIV-1 seroconversion [RR = 3.79, 95% confidence interval (CI) = 1.44 to 9.93,  $P = 0.007$ ]. The decrease in risk of HIV-1 infection associated with HIV-2 seropositivity was again demonstrated (RR = 0.23, 95% CI = 0.06 to 0.78,  $P = 0.02$ ). The protective effect of HIV-2 seropositivity, irrespective of CD4<sup>+</sup> cell count, was consistent, even though a lower CD4<sup>+</sup> cell count was a significant predictor of HIV-1 seroconversion (16).

A potential source of bias in the data could have been differential losses to follow-up. Despite a lengthy study period, the overall loss to follow-up in this cohort was 21%, and a logistic regression analysis indi-

**Table 1.** Annual incidence of HIV-1 infection. Values of IR (per 100 PYO) were determined using the sum of PYO for the group being analyzed as the denominator; the observation time for the  $n$  individuals who seroconverted to HIV-1 was truncated at the estimated date of seroconversion, that is, the midpoint between the last seronegative bleed and the first seropositive bleed. For calculation of seroincidence of HIV-1 in individuals already infected with HIV-2, the observation time was calculated as the total HIV-2-seropositive time, with truncation at the estimated date of seroconversion to an HIV dual-reactive status. The observation time for HIV-2 seroconverters was split according to the estimated date of HIV-2 seroconversion, with person-time before and after HIV-2 seroconversion evaluated as HIV-seronegative and HIV-2-seropositive person-time, respectively. Because of the time lag introduced by the back-calculation of the seroconversion dates, IRs were not calculated for the last year of the study, 1994. The 95% CI for each IR is shown in parentheses.

Calendar year	Seronegative			HIV-2-seropositive		
	PYO	$n$	IR	PYO	$n$	IR
1985	110.01	0	0.00	14.74	0	0.00
1986	229.62	0	0.00	43.71	0	0.00
1987	284.03	4	1.41 (0.53 to 3.75)	59.85	1	1.67 (0.24 to 11.86)
1988	306.77	4	1.30 (0.49 to 3.47)	67.55	0	0.00
1989	336.93	5	1.48 (0.62 to 3.57)	85.64	1	1.17 (0.16 to 8.29)
1990	349.63	10	2.86 (1.54 to 5.32)	97.92	1	1.02 (0.14 to 7.25)
1991	313.38	19	6.06 (3.87 to 9.51)	99.61	2	2.01 (0.50 to 8.03)
1992	274.43	13	4.74 (2.75 to 8.16)	93.77	0	0.00
1993	205.75	6	2.92 (1.31 to 6.49)	94.77	2	2.11 (0.53 to 8.44)
Total	2410.55	61	2.53 (1.97 to 3.25)	657.56	7	1.06 (0.51 to 2.22)

**Table 2.** IRs (per 100 PYO) and RRs (ratio of HIV-2-positive IR to HIV-negative IR) for HIV-1, gonorrhea, and syphilis, with 95% CIs (in parentheses). Values of IR were determined as in Table 1. If two positive gonorrhea or syphilis tests occurred within 6 months of each other, the second positive test was not considered an incident infection.

Serostatus	PYO	HIV-1	Gonorrhea	Syphilis
		IR		
HIV-2-positive	657.56	1.06 (0.51 to 2.22)	5.76 (4.19 to 7.91)	6.97 (5.22 to 9.30)
HIV-negative	2410.55	2.45 (1.90 to 3.16)	3.82 (3.11 to 4.68)	4.98 (4.16 to 5.95)
		RR		
HIV-2-positive compared to HIV-negative		0.43* (0.19 to 0.92)	1.51* (1.03 to 2.20)	1.40 (1.00 to 1.97)

\* $P < 0.05$ .

cated that seronegative women were not more likely to miss a clinic visit than were HIV-seropositive women (15). We also addressed an assumption implicit in the Poisson regression model, namely that the baseline risk of HIV-1 infection remained stable over time, by means of an alternative analysis that did not depend on such an assumption. This analysis, based on a Cox proportional hazards model, gave similar results (15). The final model suggested that HIV-2-seropositive women had a significantly lower risk of subsequent infection with HIV-1 than did seronegative women, and that this protective effect was independent of CD4<sup>+</sup> cell count.

Because HIV-2 appeared to protect from subsequent HIV-1 infection, it seemed reasonable to determine whether the inverse effect could be demonstrated. A multivariate model of the effect of HIV-1 seropositivity on subsequent risk of HIV-2 infection was developed, including the same variables. This model yielded a nonsignificant RR of 1.04 for HIV-2 infection associated with HIV-1 seropositivity (95% CI = 0.33 to 3.08,  $P = 0.92$ ). The person-time of follow-up among HIV-1-infected individuals was lower than that among HIV-2-infected individuals; therefore, this analysis may lack the statistical power to detect a significant RR associated with HIV-1 seropositivity. Alternatively, infection with the more virulent and pathogenic HIV-1 may not provide the same protective mechanism against subsequent infection with the less virulent virus.

The protection observed may be a result of cross-reactive immunity to epitopes conserved between HIV-1 and HIV-2. The presentation of these epitopes in the HIV-2 context may yield a more functionally important response than does their presentation in the HIV-1 context. This possibility is supported by studies of neutralizing antibodies present in sera from HIV-2-seropositive individuals, which show higher titers of both autologous and cross-reactive neu-

tralizing antibodies than are found in sera from HIV-1-seropositive individuals (17). Antibody-dependent complement-mediated cytotoxicity (18) and cytotoxic T lymphocyte activity (19) against conserved epitopes have also been identified. In addition to these immune mechanisms, viral interference has been shown to occur in vitro. Receptor blockage, suppression of HIV replication by CD8<sup>+</sup> cells, and downmodulation of HIV-1 gene expression in a dually infected (or transfected) cell have been proposed as potential modes of cross-virus interference (20).

At least nine subtypes of HIV-1 have been identified in different areas of the world, with at least three subtypes known to circulate in parts of West Africa. These HIV-1 subtypes may differ in their transmission potential; hence, further study of the degree to which HIV-2 protects from different HIV-1 subtypes would be useful for global vaccine considerations.

Certain heterologous viral infections induce extremely effective, long-lasting immunity to subsequent pathogenic infection. Heterologous viruses have formed the basis of vaccines to protect domestic chickens from the T-lymphotropic Marek's herpes virus, to protect dogs from canine distemper virus, and to protect people from smallpox. Our data suggest that HIV-2 infection provides approximately 70% protection from subsequent HIV-1 infection. Despite the demonstrated protection potential and the lower virulence of HIV-2, the risks involved in any live virus attenuated vaccine may far outweigh the potential benefits. Therefore, we would rather suggest that the immune effector mechanisms identified in HIV-2-seropositive individuals may be targeted to cross-reactive epitopes that could be useful in HIV-1 vaccine development. Although the mechanisms responsible for this protection have not yet been elucidated, these results suggest a new course of investigation in identifying critical correlates of HIV-1 immunity.

**Table 3.** Crude HIV-1 IRs (per 100 PYO) and adjusted RRs, with 95% CIs (in parentheses). Adjusted RR estimates were derived from a multivariate Poisson regression model simultaneously adjusting for all variables. Each individual's observation time was stratified into yearly observations, along with outcome data and corresponding HIV-2 serostatus, gonorrhea infection status, age, nationality, and years of registered prostitution. Calendar year was a continuous variable; all other variables were categorized.

Variable	PYO	Incident cases	IR	Adjusted RR
HIV-2 serostatus				
Negative	2410.55	61	2.53	1.00
Positive	657.56	7	1.07	0.32 (0.20 to 0.59)*
Gonorrhea				
Negative	1170.33	18	1.54	1.00
Positive	160.48	4	1.97	1.12 (0.59 to 3.48)
Calendar year				1.25 (1.09 to 1.46)* per year

\* $P < 0.05$ .

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12. During their seronegative time, these two women would have been counted as HIV-seronegative in the PYO total until their estimated seroconversion dates, and they would have been scored as HIV-1 seroconverters. However, they are also HIV-2 seroconverters, yet their HIV-2-seropositive status is not equivalent to that of other HIV-2-seropositive individuals in the study because they are not at risk for HIV-1. Including them in the analysis might have resulted in an overestimate of HIV-1 incidence and an overestimate of the HIV-2 protective effect. Thus, by excluding these individuals our estimate is conservative in this regard.
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16. Multivariate analysis was conducted using observations only from women with higher CD4<sup>+</sup> cell counts (>800/mm<sup>3</sup>); the RR associated with HIV-2 seropositivity was 0.26 (95% CI = 0.08 to 0.83,  $P < 0.04$ ). Among women with lower CD4<sup>+</sup> cell counts, HIV-2 seropositivity yielded an RR of 0.19 (95% CI = 0.11 to 0.85,  $P < 0.04$ ).
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