HIV-2 and Natural Protection Against HIV-1 Infection

Karin Travers et al. report that infection with HIV-2, an apparently less virulent strain of the human immunodeficiency virus (HIV), provided natural protection, estimated at approximately 70%, against infection with HIV-1 in a cohort of female sex workers in Senegal (1). This finding rests on the significantly lower HIV-1 incidence rate over a 9-year period among HIV-2–infected women [1.06 per 100 person-years of observation (PYO) in tables 1 and 2 of the report (1)] than among HIV-seronegative women [shown as 2.53 per 100 PYO in table 1 but 2.45 per 100 PYO in table 2 of the report (1)]. However, in a 1994 paper (2) the same research group reported an HIV-1 incidence rate of 1.11 per 100 PYO in the same general population of HIV-seronegative female sex workers-followed over roughly the same period. Had the HIV-1 incidence rate among seronegative women in the 1995 report (1) been similar to that reported the year before, no reduced HIV-1 incidence would have been found among HIV-2–infected women relative to uninfected women, and therefore there would have been no suggestion of natural protection.

A comparison of the data from these two papers (1, 2) (Table 1) shows that, while the numbers of women seroconverting annually in the two studies were identical through 1989 and similar in 1990 and 1991 (differences in 1992 and 1993 were presumably due to the longer follow-up period in the later paper), the 1995 report (1) includes only about half as many seronegative women (618 women contributing 2410 PYO) as reported in the earlier paper (2) (1277 women contributing 4141 PYO). The 1994 paper (2) appears to report on all initially HIV-seronegative female sex workers enrolled in the Dakar study clinic. The time observed before their latest serologic test served as the denominator, while the number of seroconversions in the group was the numerator for computing the HIV-1 incidence rate. The 1995 report (1) followed only a subset of the earlier study population, limited to those women with HIV-1 or HIV-2 infection (apparently including both initially prevalent cases and cases incident during follow-up) along with two randomly selected seronegative women for each infected woman, matched on the basis of age, nationality, and number of years of registered prostitution. This procedure seems to have reduced the number of seronegative women followed up (and the corresponding PYO) by a factor of about two, yet included virtually all the seronegative women who became HIV-1 positive. It seems highly unlikely to us that truly random sampling would have brought all the seroconverters into the smaller group, and a selection bias favoring seroincident HIV-1 cases may have occurred. Such a bias would artifactually elevate the HIV-1 incidence rate in the seronegative group, giving by comparison the appearance of a lower HIV-1 incidence in the HIV-2 group.

Because of this uncertainty, the evidence is currently insufficient to suggest that HIV-2 infection protects against HIV-1. We hope Travers et al. will clarify how virtually all the seroconverters from the larger study population were selected into their seronegative comparison group. To minimize the effect of potential selection biases, we would encourage the authors to recalculate the HIV-1 incidence rates in their unique and valuable study population using a retrospective cohort analysis, analogous to evaluating vaccine efficacy. For this recalculation, the HIV-2 cohort would remain the 187 women with prevalent or incident HIV-2 infection. The comparison cohort, however, should be limited to those 374 women who, while still seronegative, were matched 2-for-1 to the HIV-2 cases, rather than the 618 women that were used. Such a recalculation could determine whether in fact HIV-1 incidence was influenced by pre-existing HIV-2 infection and therefore whether any natural protection may have occurred.

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2. P. J. Kanki et al., Lancet 343, 943 (1994).

Response: Greenberg et al. incorrectly assume that data excerpted from our comparative HIV incidence study published in 1994 in Lancet (1) can be directly compared with excerpted data from our 1995 report in Science, which evaluated HIV-2 protection (2). The protective effect of HIV-2 cannot be assessed with the use of crude incidence estimates. The baseline risk for HIV-1 infection must be comparable between the HIV-negative and HIV-2–positive groups, and this was accounted for in our study design and analysis (2). Further, these two studies (1, 2) were distinct in the research questions that each addressed, criteria for subject enrollment, and follow-up and analysis. The HIV-2 protection study (2) population was composed of registered sex workers; some of these women represented a subset of the study population described in Lancet (1), but there are three important differences between the two studies. First, HIV-positive individuals were eligible for enrollment in the HIV-2 protection study (2), while the Lancet study (1) excluded them. (Each enrolled HIV-positive woman was further matched to two HIV-negative women to achieve comparable data with regard to follow-up and baseline risk for

Table 1. Comparison of data about HIV-1 infection from two studies of the same basic population followed over roughly the same period. PYO, person-years of observation. IR, incidence rate.

Sample Year	Travers et al. (1)			Kanki et al. (2)		
	Sero-converters	PYO	IR	Sero-converters	PYO	IR
1985	0	110	0	0	187	0
1986	0	229	0	0	448	0
1987	4	284	1.41	4	552	0.72
1988	4	307	1.30	4	609	0.66
1989	5	337	1.48	5	704	0.71
1990	10	350	2.86	9	732	1.23
1991	19	313	6.06	18	640	2.81
1992	13	274	4.74	6	274	2.19
1993	6	206	2.92			
Totals	61	2410	2.53	46	4141	1.11

Table 1. Adjusted HIV-1 rate ratios comparing HIV-2–positive women to HIV-negative women. Ratios derived from multivariate Poisson regression models simultaneously adjusting for HIV-2 status, years of registered prostitution, age at registration, nationality, study year, CD4$^+$ lymphocyte count, and incident sexually transmitted disease.

Study design and analysis	HIV-2 serostatus	No. of subjects	Adjusted rate ratios	95% CI	Fraction protected (%)
All registered female sex workers	Negative	1264	1.00		
	Positive	199	0.36*	(0.13 to 0.99)	64
Sensitivity analysis	Negative	1264	1.00		
	Positive	199	0.48*	(0.24 to 1.00)	52
Cohort analysis matched 2:1	Negative	374	1.00		
	Positive	187	0.27*	(0.10 to 0.76)	73
Updated cohort analysis matched 2:1	Negative	398	1.00		
	Positive	199	0.26*	(0.09 to 0.72)	74

*$P < 0.05$.

HIV-1 infection between subject groups.) Second, differences in the specific enrollment criteria of the two studies meant that 305 HIV-negative women from the *Lancet* study did not meet initial enrollment criteria for the HIV-2 protection study and so were excluded. Third, women in the HIV-2 protection study that did not attend their scheduled visits were actively followed by a team of physicians and clinic workers. This active follow-up was not part of the protocol of the *Lancet* study (*1*), in which we stated that loss to follow-up might have resulted in an underestimate of HIV-1 incidence among HIV-negative women.

Greenberg et al. prematurely conclude that our matching procedure (*2*) may have resulted in a selection bias that would be responsible for the protective effect of HIV-2. To address these concerns, we performed the HIV-2 protection analysis on a nonmatched study population that included 199 HIV-2–positive (12 added from 1994 through 1995) and 1264 HIV-negative women. Seven women became dually infected among the 199 HIV-2–seropositive women, and 83 women seroconverted to HIV-1 among the 1264 HIV-seronegative women. The adjusted incidence rate ratio (IRR) for HIV-2–positive women was 0.36 (95%CI = 0.13 to 0.99), which was statistically significant ($P < 0.05$) (Table 1). Because the *Lancet* study had clearly shown Ghanaian nationality as a predictor of HIV-1 seroconversion (adjusted RR 2.70; 95%CI = 1.28 to 5.72) (*1*), we performed a sensitivity analysis to evaluate its potential effect on HIV-2 protection. All HIV-negative and HIV-2–positive Ghanaians that were lost to follow-up were coded as HIV-1 seroconverters, the adjusted IRR for HIV-2–positive women was 0.48 (95%CI = 0.24 to 1.00), which was statistically significant ($P < 0.05$) (Table 1). This analysis demonstrates the protective effect of HIV-2 even

when we account for potential differential risk in those who were lost to follow-up.

As suggested, we analyzed 187 HIV-2–positive women; each one was compared with two randomly selected HIV-negative women ($n = 374$) matched on age, nationality, and years of registered prostitution. This is a lower number of HIV-negative women than reported (*2*) as a result of our removing: all negative women matched to HIV-1–positive women, all HIV-1 seroconverters that were not originally matched as seronegative women, and HIV-2 seroconverters who contributed seronegative person-time. Seven women became dually infected among the 187 HIV-2–seropositive women, and 41 women seroconverted to HIV-1 among the 374 HIV-seronegative women. We constructed a multivariate Poisson regression model as described in our report (*2*), and the adjusted IRR for HIV-2–positives was 0.27 (95%CI = 0.10 to 0.76), which was statistically significant ($P < 0.05$) (Table 1). When we added new data from 1994 through 1995, the adjusted IRR for HIV-2–positive women was 0.26 (95%CI = 0.09 to 0.72), which was statistically significant ($P < 0.05$) (Table 1).

When we excluded the CD4$^+$ lymphocyte count variable, the adjusted IRR for HIV-2–positive women was 0.34 (95%CI = 0.15 to 0.76), which was statistically significant ($P < 0.05$). These analyses, analogous to those performed for evaluation of vaccine efficacy, suggest that approximately 64 to 74% of the women with HIV-2 are protected against HIV-1.

This reanalysis of our data, with two additional years of observation and alternative methods of analyses, shows that HIV-2–positive women were at lower risk of HIV-1 infection than were HIV-negative women, with an adjusted IRR ranging from 0.48 to 0.26 (52 to 74% protection), which is consistent with our earlier results (*2*). In all of our analyses, a statistically significant protective effect of HIV-2 was found. Further studies on the mechanism of how HIV-2 infection appears to protect over half of the population at risk for HIV-1 should assist in the future design of vaccine candidates that are broadly protective across HIV subtypes.

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Modeling HIV Concentration During Acute AIDS Infection

In a recent report (*1*), Andrew N. Phillips applies a mathematical model of population dynamics to investigate the causal relationship between changes in plasma viraemia and CD4$^+$ T lymphocyte numbers in the lymphoid system during the acute phase of human immunodeficiency virus (HIV) infection. A picture emerged from this hypothetical analysis that appeared to mirror the changes that occur during the initial stages of natural HIV

infection—a massive burst of plasma viraemia that reaches a transient peak, followed by a rapid decline in virus concentrations. A central feature of the model was the lack of compensation for any influence that the immune response may exert during primary infection, as reflected by the use of a constant rate of removal of both free virions and virus-infected cells. The net outcome from this model predicted a substantial decline in numbers of