

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.

Phyllis J. Kanki
Geoffrey Eisen
Karin U. Travers
Richard G. Marlink
Myron E. Essex
Harvard AIDS Institute,
Boston, MA 02115, USA
Chung-cheng Hsieh
Department of Epidemiology,
Harvard School of Public Health,
Boston, MA 02115, USA
Souleymane MBoup
Cheikh Anta Diop University,
BP 7325, Dakar, Senegal

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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

activated, uninfected CD4⁺ T lymphocytes that would be available for HIV infection de novo, and it was concluded that this decline could account for the subsequent drop in plasma virus concentrations, as it would be increasingly more difficult for free circulating virus to find suitably activated host cells to infect and in which to replicate.

First, we would like to discuss the models defining criteria, from which potentially misleading conclusions are drawn. The equations only account for HIV infection of activated CD4⁺ T lymphocyte subpopulations. Yet, previous genotypic and phenotypic characterization of HIV-1 isolates during primary HIV-1 infection has shown that the initial HIV-1 population in recent seroconverters is relatively homogenous and consists predominantly of macrophage-tropic and nonsyncytium-inducing (NSI) isolate variants, which are suggested to arise as a consequence of selective transmission, or expansion of these variants, or both within the new host (2). These previous results suggest that the predominant cell types infected during primary HIV infection are derived from the monocyte-macrophage lineage, an important consideration with regard to viral adaptation, as the majority of newly infected individuals acquire HIV through heterosexual transmission, where CD4⁺ macrophages or antigen-presenting cells in the mucosal barrier would represent the major susceptible cell type. Similar selective expansion of monocyte-macrophage NSI variants has been reported to occur in hemophiliacs (during initial HIV infection), who are presumably infected by the parenteral route of transmission (3). Surely, if these cell subpopulations, which seem to play a pivotal role in primary HIV infection and viral dissemination, were included in the empirical equation used by Phillips, a much greater reservoir of appropriately activated or susceptible CD4⁺ cells would become available for infection, and as a consequence, comparatively higher rates of viral replication would be maintained for a greater period of time in the absence of any effective immune response (4). Support for a central role for CD4⁺ cell types other than T lymphocytes is reflected by the heterogeneous clinical manifestations of primary HIV infection with gastrointestinal, dermatological, neuropathic, and lymphoid tissue involvement arising from the widespread dissemination of HIV (5).

Second, the most marked increases in absolute CD8⁺ T cell numbers—with selective expansion percentage of CD8⁺ T cells expressing activation markers such as human leukocyte antigen (HLA)–DR, CD38, and CD11a (6)—occur in those individuals exhibiting the most pronounced clinical

signs associated with acute HIV infection and is associated with poor prognosis and disease progression (7). On the basis of the observations that such immunological changes do occur during primary infection and correlate significantly with disease activity later on, it is difficult to accept the suggestion (1) that these events do not play a significant role in the resolution of the primary HIV syndrome itself, particularly because the frequencies of potentially infectable CD4⁺ cell subsets, and hence viral burden, may be substantially greater than accounted for in this empirical analysis if not controlled by the introduction of an effective immune response. The susceptibility to initial HIV infection varies considerably between individuals, and some studies have suggested that this is directly linked to the degree of inherent immune activity and immunogenetic background of an individual before the exposure to HIV (8). Furthermore, the demonstration that certain HIV-exposed individuals who remain seronegative and polymerase chain reaction–negative elicit HIV-specific CTL (cytolytic T lymphocyte) responses suggests that an immune response can be induced effectively in a much shorter window of exposure (9). If these CTL responses can be deemed to be protective in these cases, then surely similar responses initiated during the relatively extended time frame of primary infection (up to 3 months) also play a central role in containing viral replication and are not merely initiated as a wholly nonfunctional consequence of HIV infection (as suggested in a caveat to this analysis in the report).

It is refreshing to read a report that questions the basis of currently accepted scientific dogma. Only in this way can we extend our understanding of HIV infection and immunopathogenesis. However, since it is now more widely accepted that the highly variable course of HIV-1 infection and disease is determined by complex interactions between a highly variable pathogen and a multivariate host immune system, it is logical to suggest that this process begins at the initial point of infection.

Susan E. Wilson
John A. Habeshaw
John S. Oxford
Academic Virology,
The London Hospital Medical College,
Whitechapel, London, E1 2AD,
United Kingdom

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Response: Wilson *et al.* suggest that because HIV-1 isolates derived during primary infection are often macrophage-tropic and non-syncytium-inducing (NSI), most cell-free virus is likely produced by cells from the macrophage-monocyte lineage. However, macrophage-tropic isolates are commonly found throughout much of the asymptomatic phase of infection (1). That most cell-free virus is derived from CD4 lymphocytes that die rapidly on active infection is suggested by the rapid dynamics of changes in concentrations of cell-free virus on administration of antiretroviral drugs (2, 3), together with the correlation between treatment-induced changes in plasma virus concentrations and CD4 lymphocyte counts (4–6). Nonetheless, the hypothesis that the decline in plasma virus concentration in primary HIV infection may be a result of depletion of susceptible cells is general and, given that cells producing most plasma virus are short-lived (2, 3), remains relevant if a proportion of these are assumed to be of monocyte-macrophage lineage.

Wilson *et al.* suggest that the fact that there is an association between CD8 cell activation early in HIV infection and a poor prognosis argues that these early activation events play a significant role in the resolution of the primary HIV syndrome. It is difficult to understand, however, why those patients with the greatest immunologic activity in this regard should experience the most rapid progression of HIV infection (7). On a further point, the finding of HIV-specific CTL responses in some HIV-exposed seronegative individuals (8), although of great interest, does not in itself indicate that they necessarily “play a central role in containing viral replication.”

Findings from the mathematical models (9) have not disproved the concept of immune control of HIV during primary infection. They have merely pointed to an alternative explanation for the decline in virus which is no less consistent with existing data. The degree to which the decline can be attributed to any HIV-specific immune response, rather than to popu-

lation dynamics, will only be resolved when much larger numbers of individuals in this early stage of infection have been examined, with discriminating single cell studies in both the blood and tissues.

Andrew N. Phillips
HIV Research Unit,
Department of Primary Care and
Population Sciences,
Royal Free Hospital School of Medicine,
Rowland Hill Street,
London NW3 2PF, United Kingdom

Rate of Killing of HIV-Infected T Cells and Disease Progression

In a recent study by Steven M. Wolinsky *et al.* (1), of which one of us, A.U.N., was a co-author, several biological parameters were found to be associated with the rate of disease progression in six individuals infected with human immunodeficiency virus (HIV). Rapid CD4 cell depletion and disease progression was associated with low anti-HIV cytolytic T lymphocyte (CTL) precursor frequency, high viral loads, and slow accumulation of genetically diverse viral forms. It was suggested (1, 2) that these measures could be explained by the effectiveness of the immune system in killing infected cells, and that a successful immune pressure resulted in adaptive evolution of HIV. An additional correlation with disease progression that was observed was a preponderance of unspliced cellular HIV messenger RNA (mRNA) as compared to spliced mRNA in rapid progressors. Current hypotheses suggest (3) that the observed differences in the ratio of unspliced to spliced RNA (U/S RNA ratio) among patients is accounted for by the patients having viruses with different viral properties.

The difference in the ratio of spliced to unspliced RNA might also be explained by differences in the effectiveness of the cellular immune response. HIV RNA production by an infected cell goes through several phases. In the early phase the viral transcript gets multiply spliced to express the early regulatory genes and there is no export of unspliced RNA from the nucleus. Only in the late phase of viral expression does unspliced RNA get exported to the cytoplasm (4). The U/S RNA ratio is therefore strongly dependent on the ratio of cells in the early phase, expressing only spliced RNA, versus the cells in the late phase, expressing also unspliced RNA. Faster killing of the cells in the early phase will not change the U/S RNA ratio, because the number of cells in the later phase depends on the number of cells that complete the early expression phase. Thus, if more early phase cells are killed, the amounts of both spliced and unspliced intracellular mRNA will be reduced proportionately. On the other hand, faster killing of the cells in the later expression phase will significantly re-

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duce the amount of unspliced intracellular mRNA. Therefore, faster killing of infected cells in slow-progressors that have better CTL responses will give rise to a relatively low U/S RNA ratio. Slower killing of infected cells in rapid progressors will give, according to this hypothesis, higher U/S RNA ratio. This is consistent with higher U/S RNA ratios observed (1, 3, 5) in rapid progressors, which is associated (1) with weaker cellular immune responses.

This same hypothesis could explain the longitudinally observed (1, 3, 5) increase of the U/S RNA ratios as being related to weakening of the cellular immune response during the period of disease progression (2). The hypothesis suggested here is in line with the one suggested by Wolinsky *et al.*, that differences in the CTL response are the basis for differences in the rate of disease progression in these patients. A quantitative analysis of the hypothesis, using a mathematical model, gave the same results as described above (6).

Martijn A. Huynen
Avidan U. Neumann
Santa Fe Institute,
1399 Hyde Park Road,
Santa Fe, NM 87505, USA and
Theoretical Biology,
Los Alamos National Laboratory,
Los Alamos, NM 87545, USA
E-mail: aun@t10.lanl.gov

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S. E. Wilson, J. A. Habeshaw, J. S. Oxford and A. N. Phillips

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