The protective effect of HIV-2 infection: implications for understanding HIV-1 immunity

Phyllis J. Kanki[a] and Sarah Rowland-Jones[b]

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HIV-2 was first described in 1985 in West Africa on the basis of its antigenic relationship to HIV-1 and the SIV [1,2]. Since that time, several international research collaborations have sought to understand the pathogenicity of this closely related HIV virus and the impact of its interaction with the prototype HIV-1 infection *in vivo*. Coexisting in West Africa with HIV-1, HIV-2, by contrast generally demonstrates an attenuated phenotype for transmission and disease [3,4]. In rural Guinea Bissau, a more bimodal outcome has been described with HIV-2 progressors indistinguishable from HIV-1 progressors, and HIV-2 controllers (35–40%) maintaining undetectable viral load for 10–15 years, with a normal life expectancy [5]. In 1995, the concept that HIV-2 might protect from HIV-1 infection was raised from long-term studies of the registered sex worker cohort in Dakar, Senegal [6,7]. The generalizability of these findings was questioned by studies from Ivory Coast, Guinea Bissau and the Gambia [8–10]. Continued virologic and immunologic studies of HIV-2 over the past three decades have continued to support the attenuated phenotype or unique 'elite control', which remains of interest in our quest to better understand the immunopathogenesis of HIV-1, identify correlates of protective immunity and develop appropriate interventions [11].

Esbjornsson *et al.* [12], in this issue of *AIDS*, report on the longer survival time for HIV-1 and HIV-2 dually infected individuals than for individuals who were singly HIV-1 infected. HIV-2 and HIV-1 dual-infected individuals with an HIV-2 infection preceding the HIV-1 infection had lower mortality than HIV-1 singly infected individuals. The study was based on a well characterized longitudinal cohort of police followed for more than 20 years in Guinea-Bissau, a country with the largest documented HIV-2 infection in the 1980s, with up to 8% adult prevalence [13]. These authors have previously reported that subjects who had HIV-2 infection prior to the acquisition of HIV-1 had a significantly longer time to the development of AIDS compared to subjects acquiring HIV-1 in the absence of prior HIV-2 infection [14]. The current study is distinct from the previous published study, distinguished by the outcome of all-cause mortality, longer follow-up and the dissection of the sequence of infection resulting in dual infection.

Prince *et al.* [15] conducted a literature review and meta-analysis and found no evidence of delayed progression to death in dually infected individuals. Esbjornsson *et al.* [12] discuss some of the possible explanations for the apparent discrepancy in these studies. The analysis by Prince *et al.* [15] included seven West African studies, which were conducted largely on seroprevalent patients, with a focus on hospitalized patients. The seven studies had differing study designs, widely variable loss to follow-up rates and generally shorter observation times [15]. Esbjornsson *et al.* [12] observe that the rate of $CD4^+$ T-cell decline is similar between single and dual-infected participants, whereas the absolute levels at the presumed date of infection are quite distinct; therefore, studies without a reliable

[a]Department of Immunology & Infectious Disease, Harvard School of Public Health, Boston, Massachusetts, and [b]Nuffield Department of Medicine, NDM Research Building, Old Road Campus, Oxford, UK.

Correspondence to Phyllis J. Kanki, Department of Immunology & Infectious Disease, Harvard School of Public Health, 651 Huntington Ave, Boston, MA 02115, USA.

E-mail: pkanki@hsph.harvard.edu

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seroconversion date will inevitably lead to misinterpretation. Finally, the seven studies included in the meta-analysis varied widely in the sex ratio of study participants, ranging from 14.8 to 100% women [15]. The Guinea Bissau police cohort is somewhat unusual in having a majority of HIV-2-infected individuals that are men, inviting speculation that sex could play a role in the disparate results [12,14]. It is also worth considering that differences between different epidemiological studies may reflect the extensive host genetic diversity in this part of Africa, particularly in the human leukocyte antigen (HLA) and killer immunoglobulin-like receptor (KIR) genes that are known to influence the outcome of HIV-1 and HIV-2 infection and that differ significantly between different ethnic groups in West Africa [16].

The methods for classification of HIV dual-infected individuals have differed between research groups for decades [17]. Although equally sensitive and type-specific PCR diagnosis of proviral DNA should be considered the gold standard, this type of assay has been rarely verified or widely used [17,18]. Three of the seven studies in the meta-analysis used PCR to augment serologic diagnoses [15]. As Esbjörnsson *et al*. [12] indicate, the evaluation of sequential serum samples analysed with the same assay that changed from a mono-infected HIV-2 to dual HIV-2 and HIV-1 reactivity should improve the accuracy of the HIV-dual diagnosis [14]. The additional data from PCR studies provided in the digital content material are also reassuring; although potentially three of 29 individuals may have been misclassified, a reanalysis did not alter the conclusions of the study [12].

Although the implications of HIV-2 and HIV-1's interactions *in vivo* have now been debated for decades, there are significant virologic and immunologic studies that could explain how prior HIV-2 infection might alter the pathogenesis of HIV-1 disease progression. *In vitro*, stimulated HIV-2-infected lymphocytes express beta-chemokines that inhibit HIV-1 infection with CCR5 viruses [19,20]. In addition to HIV-2's demonstrated robust cytotoxic lymphocyte responses [21,22], accompanying granzyme production would elicit beta-chemokines resulting in the demonstrated downregulation of the CCR5 receptor on $CD4^+$ bearing cells [23], rendering the target for HIV-1 and HIV-2 viruses less susceptible to infection. Intriguingly, in the cohort studied by Esbjornsson *et al*. [14], HIV-1 disease progression was most attenuated in HIV-2-infected individuals who had stable asymptomatic disease. This raises the possibility that HIV-1 was inhibited by immune mechanisms associated with HIV-2 control and delayed disease progression, for which $CD8^+$ gag-specific T-cells would be the most obvious candidate, a response that is absent in more than 50% of those with progressive disease [22]. Extensive cross-reactivity has been demonstrated between HIV-1 and HIV-2 epitopes, particular for $CD4^+$ and $CD8^+$ T-cells directed against the most conserved regions of the gag proteins [24]. It is therefore plausible that the potent and unusually high avidity T-cell responses [25] elicited by HIV-2 contribute to the control of HIV-1 replication *in vivo*. Although HIV-2 infection is also characterized by a very potent neutralizing antibody response that sometimes cross-neutralize HIV-1, the neutralization of HIV-1 is less potent and there is no relationship between neutralizing activity and clinical status [26,27]. HIV-2 infection results in a low-level persistent viral infection [28], which elicits robust humoral, innate and adaptive cellular immunity; cross-reactivity likely inhibits the replication of HIV-1 and ensuing disease progression. This may also explain why the diminished disease phenotype is not apparent in individuals who were infected with HIV-1 prior to HIV-2 [12]. The mounting of the immune response to HIV-2 would be critical to the protective effect for both HIV-1 immunopathology and the development of disease.

Since its initial discovery, studies of HIV-2 in infected individuals in West Africa have provided compelling evidence for potential mechanisms that may be critical to the pathogenicity of HIV viruses in general. At the time of its discovery, HIV-2 was shown to be endemic in West Africa, with more sporadic distribution globally, often linked to the former Portuguese sea trade [29]. However, its prevalence has been diminishing over the past 30 years and it is likely that the opportunity for further in-vivo study may soon disappear [30,31]. The results of the study by Esbjornsson *et al*. [12] reinforce the critical need for research to further investigate the virologic and immunologic mechanisms responsible for HIV-2's attenuated phenotype and protection from HIV-1 disease with significant implications for HIV therapy and vaccine development.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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