# Reply to Jefferys: Declining HIV virulence

We are grateful for this opportunity, in responding to Jefferys (1), to discuss further the nature of the relationship between HIV replication capacity and disease progression.

The published studies [of which seven are cited in Payne et al. (2)] examining the relationship between viral replication capacity (VRC) and viral setpoint, CD4 count, and CD4 decline, overall, have painted a consistent picture: High VRC is associated with high viral setpoint, with low CD4 count, and with more rapid CD4 decline. However, there is some variability in these studies. This is related, in part, to the fact that VRC may only explain up to 33% (95% confidence interval 20–46%) (3) of HIV setpoint variance. A second factor contributing to variation between studies relates to critical differences in the cohorts studied and study design.

The longitudinal study by Prince et al. (4), for example, tracking the disease course from acute infection in transmission recipients in whom the precise virus transmitted was ascertained, provides an optimal means of assessing the impact of the VRC of the transmitted virus on disease outcome. In that study, the VRC of the transmitted virus correlated with viral setpoint in the recipient ($P = 0.02$) and also with the rate of CD4 decline ($P = 0.029$). The ability of VRC to be associated with CD4 decline from measurements only made during chronic infection is compromised by the fact that compensatory viral mutants that increase VRC are characteristically selected over time (5). There is evidence (4, 5) that the VRC of the early, transmitted virus may therefore be more strongly associated with CD4 decline and disease outcome than the VRC of virus obtained during chronic infection.

The findings from the two selected publications mentioned by Jefferys are therefore not difficult to reconcile with those of Payne et al. (2). Indeed, the correlation between absolute CD4 count and VRC in the Botswana cohort ($r = -0.31$, $P = 0.01$; $n = 63$) is highly consistent with the other studies published, including the study of 45 individuals from acute infection, in which VRC was linked with CD4 decline ($r = -0.25$, $P = 0.09$).

It is important to note here that, although host and virologic factors contributing to HIV disease outcome may be considered as separate entities, HLA is both the dominant host genetic factor influencing HIV disease outcome and the principal force driving viral sequence variation and differences in VRC (6). The association between decreasing VRC and the accumulation of escape mutants associated with protective HLA alleles such as HLA-B*57 is a consistent feature of the literature, including the recent study in Botswana and Durban (2).

Finally, it has been suggested that long-term follow-up of patients with HIV disease would provide a better means than VRC of assessing the direction of HIV virulence over the course of the epidemic. However, the reality is that it will be increasingly difficult in the future to assess changing virulence over time other than by VRC, as more widespread access to antiretroviral therapy (ART) and earlier initiation of ART before CD4 decline will, happily, prevent most disease progression.

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**1** Jefferys RJ (2015) Evidence for HIV weakening over time. *Proc Natl Acad Sci USA* 112:E2118.

**2** Payne R, et al. (2014) Impact of HLA-driven HIV adaptation on virulence in populations of high HIV seroprevalence. *Proc Natl Acad Sci USA* 111(50):E5393–E5400.

**3** Fraser C, et al. (2014) Virulence and pathogenesis of HIV-1 infection: An evolutionary perspective. *Science* 343(6177):1243727.

**4** Prince JL, et al. (2012) Role of transmitted Gag CTL polymorphisms in defining replicative capacity and early HIV-1 pathogenesis. *PLoS Pathog* 8(11):e1003041.

**5** Brockman MA, et al. (2010) Early selection in Gag by protective HLA alleles contributes to reduced HIV-1 replication capacity that may be largely compensated for in chronic infection. *J Virol* 84(22): 11937–11949.

**6** van Dorp CH, van Boven M, de Boer RJ (2014) Immuno-epidemiological modeling of HIV-1 predicts high heritability of the set-point virus load, while selection for CTL escape dominates virulence evolution. *PLOS Comput Biol* 10(12):e1003899.

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