

**Accelerated Immunodeficiency by anti-CCR5 Treatment in HIV Infection**

*One of the great mysteries of HIV is how, in about 50% of Western patients (i.e., those with Subtype B), a more deadly HIV strain emerges late in infection. The new strain, known as X4, differs from its predecessor R5, because X4 only infects CD4<sup>+</sup> T cells (“helper” immune cells necessary for orchestrating one’s overall immune response) displaying the receptor CXCR4, whereas R5 only infects CD4s displaying CCR5. Because CXCR4 and CCR5 are found on different CD4s, X4 depletes an additional set of critical immune cells, accelerating immunodeficiency and death. Recently, the FDA began approving drugs that selectively block R5, and some researchers have touted anti-R5 therapy alone as a potentially safer alternative to current anti-HIV drugs. An open question is whether anti-R5 treatments push HIV toward the more deadly X4 variant earlier. Using a minimal mathematical model for multi-strain HIV infection that we derive from the ground up, we show that anti-R5 treatment alone likely accelerates X4 emergence and thus immunodeficiency (Weinberger et al., 2009 PLoS Comput Biol, 5(8):e1000467). We also find that when anti-R5 treatment is combined with anti-X4 treatment or anti-HIV drug “cocktails” (known as HAART), which combat R5 and X4 equally, this risk of accelerated immunodeficiency is eliminated. But, despite X4’s late-stage ubiquity among Western/Subtype B patients, until recently X4 had not been observed in Subtype C, which represents the majority of the world’s HIV infections. We are building a model to test our theory that natural, stochastic fluctuations favor X4 as a bet-hedging adaptation and that X4’s prevalence in Subtype C will continue to rise as a result. Such an increase in X4 would caution against the prescription of CCR5 inhibitors to HIV patients worldwide in the absence of HAART, or during HAART failure.*