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Determinants of the efficacy of HIV latency reversing agents and implications for drug and treatment design

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DETERMINANTS OF THE EFFICACY OF HIV LATENCY REVERSING AGENTS AND IMPLICATIONS FOR DRUG AND TREATMENT DESIGN

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HIV eradication studies have focused on developing latency reversing agents (LRAs) to activate ('shock') HIV expression in latently infected cells so that these cells are purged through virus- or immune-mediated killing ('kill'). However, even in the presence of LRAs, HIV transcription may not be permanently turned on, and it is not clear which steps in the latency reversing process determine the rate of latent reservoir reduction. This makes evaluating the efficacy of candidate LRAs and predicting long-term treatment outcomes difficult. Furthermore, since almost all LRAs studied thus far have certain toxicities, it is likely that LRA treatment has to be structured/pulsed in a long-term treatment regimen to avoid severe side effects. How drug properties affect efficacy in structured treatment regimens is not clear, and this has to be taken into consideration when evaluating candidate LRAs.

We constructed a mathematical model that describes the dynamics of latently infected cells under both continuous and structured/pulsed LRA treatment. Using the model, we find that in addition to 'shock' and 'kill' rates, a previously understudied parameter, the rate at which HIV expression is deactivated both during and after LRA treatment, plays an important role in determining the efficacy of LRAs. This parameter determines the duration of HIV activation and the fate of activated cells. We further identified conditions/properties that allow LRAs to work better in structured treatment regimens than in a continuous treatment regimen. With the same amount of total dosing, pulsing treatment regimens can be more effective than a continuous treatment regimen when the 'shock' rate is high and the HIV deactivation rate after treatment stops is low. Therefore, in addition to increasing 'shock' and 'kill' rates, drug development should focus on drugs that minimize the HIV deactivation rate (i.e., maximize the duration of HIV expression) both during and after treatment.

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