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Optimising and understanding new HIV therapies

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One of the main focuses of HIV research today concerns allowing people living with HIV to experience prolonged periods where they do not need to remain on treatment. Current therapies are able to suppress HIV to undetectable levels, however as soon as therapy is interrupted the virus "rebounds" to pre-treatment levels and this leads to increased morbidity from HIV. This rebound likely occurs as a result of long-lived latently infected cells, which persist in spite of therapy as part of a 'latent reservoir'. Recent work has focused on reducing the size of the latent reservoir in the hope this will increase the time subjects can remain off therapy.

We set up a model of HIV remission and viral reactivation and used this to estimate both the probability of viral rebound even with a reduced latent reservoir, and also the optimal reduction in reservoir size that both minimises drug exposure, and maximises treatment effect.

Using a stochastic model we show that a treatment that achieves an average of a one-year viral remission will still lead to nearly a quarter of subjects experiencing viral rebound within the first three months and give rise to an expected 39 (95%UI 22-69) heterosexual transmissions and up to 262 (95%UI 107-534) homosexual transmissions per 1,000 treated subjects over a 10-year period.

Additionally, using a deterministic model we investigated the trade-off between increasing the average duration of remission, versus the risk of treatment failure (viral recrudescence) and the need for re-treatment. To minimise drug exposure, we find that the optimal treatment would increase the average time of viral rebound to 30 years. Interestingly, this is a significantly lower level of reduction than that required for complete elimination of the viral reservoir, but significantly longer than is currently being targeted. We show that when shorter periods are targeted, there is a real probability of viral transmission occurring in between the times at which subjects would be tested for viral rebound.

Our work shows that while therapies designed to reduce the size of the latent reservoir present a promising avenue of research, prior to widespread implementation of such strategies, the possibilities and consequences of viral reactivation from latency must be adequately considered.

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