Impact of early-stage HIV transmission on treatment as prevention

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Timely HIV treatment improves health (1) and reduces transmission (2). These individual-level benefits of HIV treatment for both clinical and preventive purposes are well established, but several questions remain about the population-level impact of HIV treatment as prevention (3). In PNAS, Eaton and Hallett (4) use a mathematical model to address one such question: Does the proportion of transmission during early HIV infection affect the impact of HIV treatment on HIV incidence?

Transmission rates are sharply elevated during the first few months of HIV infection (5), likely due to increased viral concentrations (6) and founder virus transmission advantages that facilitate transmission at a lower inoculum (7). Quantifying the corresponding fraction of transmissions attributable to contact with persons in early-stage infection has been challenging, with mathematical modeling and phylogenetic studies producing a wide range of estimates (8, 9). Because HIV treatment typically begins well after the early period of heighted transmissibility, intuition tells us that the prevention benefit of HIV treatment programs will be compromised if a large fraction of transmission events are untouched. However, this prediction has been a matter of considerable debate (10).

Eaton and Hallett (4) approach this question with a mathematical model of HIV in South Africa. They used a Bayesian approach to calibrate their model to empirical HIV prevalence data, allowing for behavioral heterogeneity across individuals, changes in risk behavior over time, and varying levels of increased infectivity during early infection. They simulated treatment interventions against a range of scenarios consistent with the observed South African epidemic, allowing analysis of the relationship between early-stage transmission and treatment impact.

Surprisingly, the amount of unabated transmission from untreated people with early infection had little impact on long-term intervention effects. To explain these results, Eaton and Hallett refer to relationships among three quantities: the rate at which incident (new) cases increase at the outset of an epidemic (the initial growth rate), the basic reproductive number (R_0), and the generation time (T_g). R_0 is the average number of secondary infections that a typical infected person causes in a wholly susceptible population, and T_g is the average time between infection of an index case and his secondary cases.

If early HIV infection plays a large role in transmission (Fig. 1*B*), then the generation time distribution will be skewed toward smaller values (more rapid transmission on average). Thus, for a given, observed growth rate, R_0 must be smaller. In contrast, if early HIV plays a smaller role (larger T_g), then R_0 must be larger to achieve the same growth rate (Fig. 1*A*). Typically, the larger the R_0, the more difficult an epidemic will be to control, because more effort is needed to reduce R_0 below the value of 1 required for elimination (11).

In the model of Eaton and Hallett, as the proportion of early-stage transmissions increased across scenarios, T_g decreased and R_0 declined. That is, although the fraction of transmission events that are not prevented by treatment is greater in scenarios with large early-stage transmission contributions, R_0 is lower. The lower R_0 at the time of

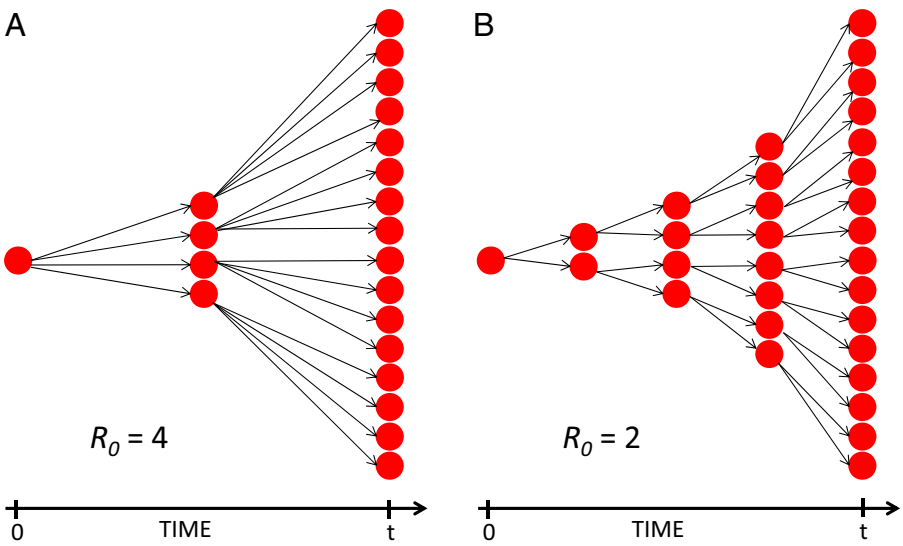

Fig. 1. Initial growth, generation time, and R_0. Red circles represent new cases. The horizontal distance between one case and those directly connected to it represents generation time T_g. The number of arrows emanating from a case represents the basic reproductive number R_0. Increases from one new case at time 0 to 16 new cases at time *t* is compatible with, for example, (*A*) two discrete generations after infection introduction, each with a longer time T_g between generations and $R_0 = 4$; or (*B*) four discrete generations, each with a shorter T_g and $R_0 = 2$. (In reality, generations will be distributed in time, but we present discrete generations to illustrate basic concepts.)

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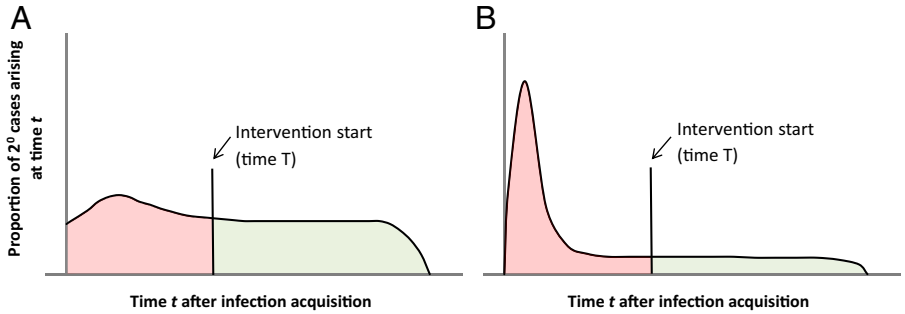

Fig. 2. Preintervention delay and intervention impact. Curves show the distribution of times within the infectious period that onward transmissions occur for two hypothetical scenarios that differ in terms of the early-stage transmission contribution. Red and green regions represent transmissions unaverted and averted by the intervention, respectively. The area under the curve represents R_0. (*A*) Smaller proportion of early-stage transmissions (higher R_0). (*B*) Higher proportion of early-stage transmissions (lower R_0). In both scenarios, earlier intervention initiation (smaller T) will result in greater fractions of averted infections, but the prevention impact will be greater in *A* than in *B* as long as early transmission is missed.

intervention initiation means that there are fewer secondary infections to prevent and the intervention is more likely to be effective. In other words, the increased role of early-stage transmission is detrimental to the intervention, but the lower R_0 appears to perfectly counterbalance this effect.

Are we to take Eaton and Hallett's model as the final word and assume that we need not worry about early HIV? We suggest that such a conclusion is premature for several reasons. First, the model predicts a moderate long-term impact of treatment: a 22% incidence reduction. That is, the intervention does not dramatically affect endemic prevalence. Near endemic prevalence, the system is relatively insensitive to changes in the reproductive number, because behavioral heterogeneity and saturation effects in high-risk groups buffer such changes. In other words, near-endemic incidence reductions are not expected to differ much across scenarios with different early-stage contributions and R_0 values.

Second, the relationship between R_0 and the effort required to control infection can be subtle for infections (like HIV) with a long infectious period and variable infectivity. In these situations, intervention performance depends not only on R_0, but more importantly on the timing of transmission and intervention initiation within the infectious period (12). Increasing HIV testing rates to achieve earlier diagnosis can be expected to reduce the preintervention delay and improve the impact of treatment (Fig. 2). However, if most secondary infections occur early in infection, then effectiveness improvements will be limited as long as early-stage transmissions are unaffected. Therefore, in scaling up treatment to achieve more than a 22% incidence reduction, the role of early infection will be crucial (13).

Finally, variability in behavioral patterns across different epidemic settings is likely to be greater than the within-epidemic variability examined in South Africa, suggesting that the model may have limited applicability outside of a generalized, heterosexual epidemic. Indeed, phylogenetic analyses among men who have sex with men in Western settings, populations in whom treatment is widespread and incidence may be increasing (14, 15), suggest large early-stage contributions (16, 17).

HIV treatment coverage is increasing, causing decreased morbidity and mortality worldwide (18). HIV incidence appears to be decreasing in some (18) but not all (14, 15, 18) settings, indicating that HIV treatment as prevention is not yet achieving maximal gains. Eaton and Hallett use a well-founded argument to conclude that early-stage transmission may not compromise treatment as prevention in some settings. However, to take treatment as prevention forward toward an elimination goal, the role of early infection cannot yet be disregarded.

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