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Biology as Population Dynamics: Heuristics for Transmission Risk

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Population-type models, accounting for phenomena such as population lifetimes, mixing patterns, recruitment patterns, genetic evolution and environmental conditions, can be usefully applied to the biology of HIV infection and viral replication. A simple dynamic model can explore the effect of a vaccine-like stimulus on the mortality and infectiousness, which formally looks like fertility, of invading virions; the mortality of freshly infected cells; and the availability of target cells, all of which impact on the probability of infection. Variations on this model could capture the importance of the timing and duration of different key events in viral transmission, and hence be applied to questions of mucosal immunology. The dynamical insights and assumptions of such models are compatible with the continuum of between- and within-individual risks in sexual violence, and may be helpful in making sense of the sparse data available on the association between HIV transmission and sexual violence.

Models of processing around the transmission event itself may be useful to shed light on questions such as:

- Are risk factors altered moderately or substantially by sexual violence, relative to consensual sex?
- Are men participating in ongoing sexual violence at particularly high risk of acquisition due to penile trauma, leading in turn to a particularly high risk in the subsequent exposure of women during acute infection of these men?
- What is the plausible range of benefit from topical or systemic post exposure prophylaxis for rape survivors, and over what time scale?
- What specific parameters (such as diffusion length scales, time scales, intermediate event counts, cell densities, etc.) might be measurable in live animal models, explants, or culture experiments, which would correspond to factors impacting the above questions?

To demonstrate these ideas, we outline a simple population dynamics-type model (1,2) which was originally developed by Welte and Walwyn (3) in order to support thinking about HIV vaccines, and then discuss how the model's mathematical form can be reinterpreted in the context of sexual violence.

Model equations cannot distinguish between any external factors which have the same effect on the model parameters. Hence, a pre-exposure prophylaxis regimen which inhibits reverse transcription could also be seen as reducing viral 'fertility'; and other active ingredients, or pharmacological actions, could induce changes (perhaps in either direction) in general inflammation of, or immune cell trafficking to, the mucosal interface. Besides sexual violence, a mature transmission model should shed some light on topical and systemic pre-exposure and post-exposure prophylaxis (PreP/PEP), vaccine development (4), hormonal contraception(5,6), treatment as prevention (TasP) (7), cervical ectopy (8), differences in viral replication due to the site of infection (9), and the biological impacts of sexual violence on the risk of HIV transmission and acquisition.

Recent work has shown that the risk of HIV transmission appears to scale non-linearly with viral load (10, 11). At levels below 100,000 RNA copies per ml, the risk of transmission can be predicted using a power law between the two variables (i.e. a linear correlation based on the logarithmically transformed data). However, at higher viral loads, further increases in RNA copies per ml are not associated with a greater risk of transmission (12, 13, 14). It has been pointed out that it is more biologically plausible, and a good fit to the data, to view this as a linear increase for smaller viral loads, and asaturation for higher viral loads.

This interpretation is consistent with the view that sexual contacts at low viral loads carry minimal risk, but extra viral load does indeed increase risk in direct proportion to viral load up to the saturation point, beyond which this effect is insignificant relative to other factors. It is plausible, and disconcerting, that violence-associated risk factors may be a substantial contributor to the risk of infection, if not epidemiologically, then potentially still at the level of the individual.

Our approach, which is rather conventional in the applied mathematical analysis of dynamical systems, and is routinely applied within the growing field of biophysics, has not, as far as we are aware, been systematically applied to the problem of HIV transmission – probably partly because movement of infectious material from person to person during intercourse is not a system readily amenable to controlled manipulation and observation. However, even working within the data-poor regime in which this field finds itself, this paradigm has the potential to assist with hypothesis generation and study design: using these tools, many regimes of diverse systems can be summarised into a far smaller number of formally distinct models, the use of which reduces technical difficulty and facilitates the transfer of intuition. We consider the development of appropriate population-dynamic models of initial

infection to be a long term process, requiring new inputs and insights into the very early stages of infection (15).

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