Why and how anti-retroviral therapy works even against HIV cell-to-cell transmission

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The discovery of direct cell-to-cell transmission of HIV, and the finding that some anti-HIV drugs don't seem active against virus that spreads that way, have caused questions and concern. A study published on February 27th in *PLOS Pathogens* tested a panel of anti-HIV drugs for their ability to suppress cell-to-cell transmission of the virus. The results reveal differences between different drugs, explain why and how anti-retroviral therapy (ART) does work, and have implications for the prevention of drug resistance as well as the development of new effective anti-HIV drugs.

Luis Agosto, Walther Mothes, and colleagues, from Yale University, New Haven, USA, established an experimental system that can measure the efficiency of cell-free and direct cell-to-cell transmission of HIV and directly compare the two modes of transmission. Cell-free transmission means new virus particles bud from one cell and then travel through inter-cellular space to find a target cell to which they bind to and subsequently infect. Direct cell-to-cell transmission involves close contact of an infected and an uninfected cell through a so-called virological synapse—an organized contact area which concentrates virus particles and cellular HIV entry points.

The researchers systematically tested the efficiency of anti-HIV drugs, including 6 different nucleoside analog reverse transcriptase inhibitors (NRTIs), 4 non-nucleoside analog reverse transcriptase inhibitors (NNRTIs), 4 entry inhibitors (ENT-Is), and 4 proteinase inhibitors (PIs), in both transmission situations. They found that while some NRTIs were unable to efficiently inhibit virus during cell-to-cell transmission, NNRTIs, ENT-Is, and PIs remained highly effective. And when they combined two inactive NRTIs, they regained potent antiretroviral activity during cell-to-cell transmission.

There are many more infectious virus particles near a target cell during cell-to-cell transmission, raising the "multiplicity of infection", or MOI, the ratio of the number of infectious particles to the number of target cells present in a defined space. When the scientists changed the MOI in their experimental system by adding more viruses to a space for cell-free transmission, they found that the different drugs behaved just like when added to cell-to-cell transmission, i.e. some NRTIs were, by themselves, ineffective in suppressing the virus. In these cases, a higher drug concentration was required to suppress an elevated number of particles. However, when two such drugs were combined, they became effective again.

These results explain how ART regimens, which are all combination therapies (e.g. of 2 NRTIs plus 1 NNRTI or PI) are capable of suppressing HIV, even if some or most of the viral transmission occurs through direct cell-to-cell contact. However, they also warn that cell-to-cell transmission could contribute to the rise of drug-resistant virus if patients don't take all their drugs as prescribed.

Because all drugs that could suppress HIV during cell-to-cell transmission were effective because they could efficiently suppress the high local MOI at virological synapses, the authors suggest that "highly effective drug regimens, either single or in-combination therapies, must exhibit MOI independence." They go on to propose that, "testing the effectiveness of antiretroviral inhibitors against increasing MOI provides a simple assay and a valuable tool for screening existing and novel drugs and future drug combinations prior to clinical testing."

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