

A Perspective on Antivirals

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Viruses are small particles that contain genetic material and in some cases enzymes, encapsulated by viral capsid protein, and sometimes covered by a lipid layer. Virus particles are incapable of replicating by themselves. For reproduction, they rely on the biosynthesis machinery of their natural plant or animal hosts, with which they have co-evolved. Viruses are causative agents involved in the development of infectious disease, including severe illnesses such as AIDS, encephalitis, hepatitis, smallpox and hemorrhagic fevers. Against certain viruses, effective vaccines have been developed that dramatically reduce the risk of infection. Vaccine trials are currently ongoing that target members of the family of flaviviruses such as Dengue virus and West Nile virus with encouraging results. The flu shot is a well-known example of a widely used vaccine, targeting influenza virus. This vaccine however is updated every year because of rapid mutations in the virus, and more often than not is only partially protective. Another hurdle for vaccine effectiveness is that treatment of patients already infected dramatically limits the protective potential. Mainly for these reasons, there is an ongoing need for the discovery and development of antiviral agents.

In broad terms, viral replication can be sub-divided into five steps: adhesion of the viral particle to the host cell; release of viral genes and enzymes, replication of viral building blocks by the host cell, assembly of viral building blocks into complete viral particles; and release of particles to infect new host cells. Antiviral compounds have been developed that target these phases of, thus effectively inhibiting the viral lifecycle. A prime example is drug development against Human Immunodeficiency Virus (HIV), the causative agent of AIDS. After merely twenty-five years, a multitude of potent drugs have been

developed that target viral integration into the host genome and viral replication among other mechanisms. Combined, treatment regimens using these drugs have resulted in a dramatic increase of life expectancy of HIV-positive individuals comparable to that of the general population. Antiviral agents have been developed to treat many more viral infections, including Human Papilloma Virus, Measles, Rubella, Cytomegalo virus and Hepatitis A, B and, more recently, Hepatitis C. With the advent of approved drugs that target this virus directly, HCV therapy will undergo a paradigm shift.

The last four to five decades have seen a remarkable increase in the development of potent antiviral agents. Combined with development of effective vaccines, these drugs have dramatically increased our arsenal for effective treatment of viral infections. There is however intrinsic risk associated with widespread use of these agents. In particular in the case of chronic infections, where patients are on medications for prolonged periods of time, adverse side effects of drug use will become problematic. Perhaps more importantly, the continued burden of drug use currently available against a wide range of viruses will put evolutionary pressure on these viruses that are exposed to them, which may result in directed evolution of resistant strains. Such evolution may be of particular concern in densely populated areas where humans come in contact with a wide variety of animal species, usually destined for human consumption. The opportunity for cross-species transmission combined with high viral mutation rates needs to be monitored on an ongoing basis. Simultaneous development of antiviral compounds needs to accelerate in order to quickly manage the outbreak of any emerging strain of resistant virus.

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