Antiviral agents have been difficult to find and we still have only a handful that meet the safety and effectiveness we have come to expect from antibacterial agents. Some, because of these limitations, are reserved for serious conditions such as HIV, hepatitis B (HBV), hepatitis C and CMV in immunocompromised patients. The widespread use of antivirals has been a phenomenon of the last one to two decades, following on from the development of the nucleoside analogues for herpes viruses. Not unexpectedly, it is only in the very recent past that we have had to confront the problems of resistance of viruses to antiviral agents, though this already poses significant management problems for some conditions.

For a number of reasons, resistance to antiviral agents is less common than has been seen with antibacterials. Firstly, most viral infections are either acute, like influenza, or a reactivation of latent infection like cold sores or shingles, so the virus is only active for a few days and there is little time for resistance to develop, and if the antiviral is used unnecessarily, such as in prescribing a neuraminidase inhibitor (NI) for a patient without influenza, there is no virus to be exposed to the antiviral. Even with long-term suppressive therapy of herpes simplex virus (HSV) infections, the periods of attenuated viral replication that occur in many people during therapy do not lead to emergence of stable resistant virus. This is very different from the situation with antibacterial agents, as there are always bacteria in the gut and on the skin and mucosal surfaces, that will be exposed and can become resistant. Interestingly, there is one partial parallel, where the use of reverse transcriptase inhibitors (RTIs) for treatment of either HIV or HBV in patients with co-infection can result in cross-resistance in the other virus.

Secondly, the acquisition of antiviral resistance often makes viruses less fit so that they disappear once the antiviral is ceased, as is usual with HSV resistant to aciclovir and penciclovir, influenza resistant to neuraminidase inhibitors and HBV resistant to lamivudine.

Thirdly, even if the viruses are fit, such as amantadine-resistant influenza A, they do not persist in communities, presumably because there is no reservoir for them that is equivalent to the human gut, skin or mucosal surfaces. However, there is growing concern that chronically immunosuppressed individuals may become significant sources for resistant viruses, as has been seen for influenza resistant to NIs. These patients could act as reservoirs for the rare, fit resistant viruses or allow time for less fit viruses to develop increased transmissibility and pathogenicity.

Fourthly, viruses neither easily exchange genetic information and never across species nor do they possess resistance plasmids, so spread of antibiotic resistance genes, as is seen in bacteria, does not occur.

However, antiviral resistance has emerged and is a particular problem in immunocompromised patients. These patients usually require long-term antiviral therapy, creating a situation where viruses continue to replicate in the presence of the antiviral, albeit at a reduced level, driving the selection of resistant mutants without an effective immune system to deal with them. There are many examples of this, including HIV resistance to RTIs and protease inhibitors (PIs), HSV resistance to aciclovir and CMV resistance to ganciclovir. A similar situation occurs in lamivudine treatment of chronic hepatitis B where, although the patients are usually not overtly immunosuppressed, their carrier state exists because of an inability of their immune system to control HBV.
Recently there has been concern about neuraminidase inhibitor resistance in influenza, particularly in Japan where several million courses of oseltamivir are used each year. Trial data indicated that oseltamivir resistance was very uncommon, but in 2004 there were reports of influenza A resistance rates of 16–18% in treated children in Japan \(^3\) possibly due to lower antiviral doses used in children. Community-wide surveillance found a resistance rate of only 0.3% \(^4\), suggesting that resistant virus was not circulating. However, a report earlier this year found high resistance rates in influenza B with suggestion of transmission of the resistant virus to close contacts \(^5\). As yet it remains unclear whether this was a localised phenomenon or an indicator of an emerging problem. Resistance to zanamivir remains a rare phenomenon. There is ongoing international monitoring of NI resistance though the Neuraminidase Inhibitor Susceptibility Network \(^5\).

Antiviral susceptibility testing is uncommon, as there is limited demand. With very few exceptions, there is no evidence for the stable circulation of resistant viruses in the community, despite extensive surveillance for aciclovir resistance in HSV and for NI resistance in influenza. Nor is the emergence of resistance a significant problem other than in specific situations of prolonged treatment of chronic infections such as hepatitis B and HIV. Therefore, resistance testing is generally undertaken only in situations of failure of therapy; e.g. the lamivudine treated patient with rising HBV-DNA levels. HIV is now the exception, as resistant viruses are known to circulate in the HIV infected community. The range of antiviral agents used is large and resistance and cross-resistance patterns are complex, so that laboratory measures of resistance are important for proper patient management.

Testing for antiviral resistance is still in its infancy. It is technically more challenging than antibacterial resistance testing because traditional methods relying on visual detection of viral growth are influenced by a large number of variables. These include the type of cell line, difficulty in maintaining stability of the medium during prolonged incubation, the nature and stability of the cell line, the varying ability of viruses to produce reliable plaques (or the inability to get reliable growth in any in vitro system), lack of standardisation of methods for determining plaque numbers, and many others. A variety of modifications have been used to detect viral growth by methods other than plaque formation, including use of monoclonal antibodies, PCR detection of product, assays of enzyme activity (e.g. neuraminidase inhibition for the NIs), but all remain technically demanding. Even the easiest combinations such as HSV and aciclovir (Figure 1), are only done in highly specialised laboratories. Determining meaningful breakpoints is difficult and will vary with the assay system used \(^6\). Therefore, there has been considerable interest in the use of genotypic methods such as sequencing to identify mutations likely to confer antiviral resistance. This has reached its highest level with the virtual phenotypes for HIV resistance, where the mutations associated with resistance to the RTIs and PIs are used to predict likely failure of therapy. It is also proving useful for determining nucleoside analogue resistance in HSV and CMV \(^3\) and NI resistance in influenza.

One approach to prevention of emergence of resistance has been the use of combinations of antiviral agents. For example, monotherapy for HIV or HBV commonly leads to resistance, so antiviral combinations are now standard for HIV treatment and are often recommended for HBV.

There remain a large number of significant viral infections for which we still have no effective antiviral agents, including most of the respiratory viruses, gastrointestinal viruses and arboviruses. Of those that we have, many are below our desired standards of both safety and effectiveness. Therefore, we can expect the supply of antiviral agents to continue to expand. We cannot afford to be complacent about antiviral resistance in the future but neither should we restrict the availability of potentially useful agents due to exaggerated fears of resistance. Of course, care should be taken to use antiviral agents appropriately, particularly in situations where stable or persisting resistant viruses may emerge.

The balancing act will continue!

**References**


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**Figure 1:** Plaque reduction assay for determining herpes simplex virus susceptibility to aciclovir. The Vero cell monolayer is stained with methylene blue.