The priorities for antiviral drug resistance surveillance and research

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The number of available antiviral drugs is growing fast. The emergence of drug-resistant viruses is well documented as a cause for drug failure. Such viruses also carry the potential for transmission, the risks for which vary according to specific viral transmission dynamics. This potential is best described for HIV and influenza. Resistance to the new generation of hepatitis C virus inhibitors is also likely to become a cause for concern. The priorities for future action to limit resistance include application of sophisticated surveillance mechanisms linked to detailed virological data, development of optimal treatment regimens (e.g. combination therapies) to limit emergence of resistance, and a focus on prevention strategies to prevent transmission.

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Introduction

The last 10 years has witnessed a major growth in the availability of specific antiviral compounds, currently standing at more than 30 within the UK. This has been fuelled by antiretroviral drug development (25 of the above drugs are targeted at HIV), although other targets include the herpes viruses, hepatitis B virus (HBV), hepatitis C virus (HCV) and influenza virus. In general, these drugs inhibit key, virally encoded enzymes of the virus in question, such as polymerase and protease. Only one drug to date, ribavirin, appears to have broad antiviral specificity, with a mode of action which may include an effect on viral genome replication fidelity.¹

As will be noted from the above list, drugs are mainly targeted against chronic infections. This is because persistent infections provide a larger ‘window of opportunity’ for drugs to impact on the natural history of infection, compared with acute viral diseases. In addition, it is easier to monitor antiviral efficacy through surrogate markers (such a blood viral load). Long-term therapy is a more attractive economic proposition for the pharmaceutical industry than a treatment course of a few days. Of note, antiviral drug therapy does not clear (eradicate) the virus for viruses which establish latency, such as HIV and HBV, and therefore the aim of the therapy is to reduce virus-associated morbidity through inhibiting replication.² In contrast, treatment of acute infections requires a different paradigm. As acute infections are, in the main, self-limiting, the cost–benefit of intervention is more difficult to demonstrate. For instance, what is the ‘value’ ascribed to an antiviral-induced reduction of pyrexia by 1 day for a mild respiratory infection? In addition, the window of opportunity for intervention is shorter; the efficacy of neuraminidase inhibitors for influenza is only demonstrable when drug is started within 24–48 h of first symptoms.³ This makes widespread use of such drugs untenable within current healthcare systems, which require general practice consultation, and diagnosis prior to drug prescription. It is for this reason that influenza pandemic plans include discussion of syndromic treatment following the identification of circulating pathogenic viruses through surveillance mechanisms.⁴

Resistance to antivirals

Antiviral therapy is very effective. For instance, it has transformed HIV from a death sentence to a chronic infection, albeit requiring lifelong treatment. Nevertheless, drug resistance has been documented against virtually all licensed drugs. Such resistance is caused by specific mutations, or sets of mutations in the viral genome, leading to an alteration of viral enzyme interaction with drug. The mechanisms of resistance nevertheless vary. For instance, HIV resistance to the nucleoside analogue reverse transcriptase inhibitors may be mediated through a reduction in drug binding to the enzyme, or, in contrast, an increased rate of drug dissociation from the enzyme following binding.⁵ Such differences underpin the cross-resistance patterns observed for specific sets of mutations. For HIV, over 50 key resistance mutations can be identified, which may be present in isolation or in combination with others. This almost infinite number of permutations is a major challenge for using genotypic data to estimate which new drugs are likely to be effective.⁶ Drugs with different resistance and cross-resistance patterns are also available for HBV, the herpes viruses [herpes simplex virus (HSV), cytomegalovirus (CMV) and varicella-zoster virus] and influenza, thus providing the rational and clinical utility of undertaking resistance testing.

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at the time of failure of first-line therapy. Efficacy of therapy is increasingly monitored virologically, for instance, blood viral load (HIV, HBV, HCV and CMV), and thus the potential emergence of resistance can be identified at an early stage. The incidence of resistance emerging on first-line therapy is highly variable between viruses and between specific drug regimens. For instance, some drugs have a higher 'genetic barrier' to resistance than others.\(^7\) Despite the current availability of antiviral agents, there continues to be a requirement for new drugs within existing classes, as well as new classes of drugs, to deal with the ever expanding number of patients infected with drug-resistant viruses. We have recently demonstrated that the mortality of HIV patients with multidrug resistance appears to be 3-fold the rate for the UK HIV cohort as a whole,\(^9\) thus justifying the urgent search for drugs against novel targets.

Transmission of resistant viruses

One of the consequences of antiviral drug resistance is the potential for resistant viruses to be transmitted to others. This is obviously the most common case for viruses with relevant transmission dynamics, and for which resistance is common. For instance, the increasing number of new HIV infections through sexual transmission will inevitably include infections from those with existing resistance (and on therapy). Similarly, the high infectivity of influenza will ensure transmission of resistant strains at times of widespread implementation of therapy. In contrast, most HBV infections worldwide occur through the vertical (mother to child) route; since treatment of women in pregnancy is uncommon (and if so, is likely to reduce the risk of transmission) and therefore transmission of resistance is less likely at a population level. Transmission of drug-resistant HSV-1 or CMV is also very rare, as a large proportion of the population is already infected as well as the fact that emergence of resistance is limited to the highly immunosuppressed population. Virtually all data on transmitted resistance thus refer to HIV.

Surveillance of antiviral resistance

Approximately 10% of new HIV infections in the UK are with viruses with at least one major resistance mutation.\(^9\) The detrimental impact of this on future drug therapy has led to widespread implementation of resistance testing prior to starting therapy, in order that first-line treatment can be individualized depending on these transmitted resistance patterns.\(^10\) It is self-evident that surveillance systems to monitor resistance in untreated individuals (i.e. transmitted resistance) are essential. Indeed, as antiretroviral therapy is rolled out to the developing world, the WHO has initiated a global laboratory network to monitor the emergence of resistance in treated and untreated HIV-infected individuals.

Future developments

There are two future developments requiring a research and surveillance response. First, a number of new drugs specifically targeting HCV polymerase and protease are likely to enter clinical practice.\(^11,12\) Unlike the current drug combination of ribavirin and interferon, these drugs will rapidly select for drug-resistant variants, particularly if used as single agents. The laboratory capacity to assess resistance and cross-resistance and studies to assess the clinical correlates of resistance will be required. Secondly, planning for a future influenza pandemic has focused on the stockpiling and use of one particular neuraminidase inhibitor, oseltamivir. In view of the potential risk of emergence and spread of resistant viruses, as described earlier, consideration needs to be given to the use of combination therapy, and the relevant in vitro, animal and clinical studies to support a combination therapy approach are urgently required.\(^13\)

In summary, the emergence of antiviral drug resistance is virtually inevitable. This provides a major clinical, laboratory and public health challenge. We have already learnt the potential for spread of these viruses from experience with HIV. A coordinated approach is required to ensure that the clinical benefit afforded by these drugs is maintained.

Transparency declarations

Dr Pillay has undertaken consultancy for Gilead Sciences, Bristol-Myers Squibb, GlaxoSmithKline, Roche and Boehringer Ingelheim.

References