Chapter 18

Strategies for the Rational Use of Antivirals

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The treatment and prevention of viral disease is a rapidly evolving field. In only a few years there has been an exponential increase in the availability of effective antiviral compounds, together with major improvements in the diagnosis and monitoring of viral infections. Predictably, development has not kept pace with the ability of these pathogens to adapt, viral resistance has been documented to almost all antivirals in current use. To minimise the emergence of resistant virus, and thus optimise patient care, it is important that antivirals are only used within an evidence-based framework.

Here, a number of issues will be discussed. First the changing profile of viral infections encountered in hospital and community settings is outlined, together with a brief overview of the antivirals currently in common use. In the next section the major problems associated with antiviral treatment are discussed, with particular emphasis on the emergence of viral resistance. The final two sections detail principles that can help to minimise these problems and aid in the rational use of antivirals in both treatment and preventative regimes.

1. THE CHANGING FACE OF VIRAL INFECTIONS AND THEIR MANAGEMENT

Viral infections have often been considered as either minor illnesses not requiring intervention, or serious conditions for which there is no effective treatment. This perspective is changing, with the importance of seemingly

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innocuous viruses increasingly recognised. For example, rhinoviruses, a cause of the common cold, are now known to be associated with severe lower respiratory disease in the immunocompromised and exacerbations of asthma (Gern and Busse, 1999; Greenberg, 2003). Similarly, though it is true that many viral infections remain untreatable, effective treatment is now available for several serious conditions, such as aciclovir in herpes simplex virus (HSV) encephalitis, ribavirin for Lassa fever, and combination antiretroviral therapy for human immunodeficiency virus (HIV).

The increase in interest in the treatment of viral disease has been perpetuated both by the emergence of new viral pathogens and by the increasing prevalence of impaired immunity, either as a result of immunosuppressive treatment regimes or AIDS. Changing behaviour patterns have also led to the opportunity for increased spread of pathogens, such as hepatitis C virus (HCV) in intravenous drug users (Mathei *et al*., 2002).

It is important to remember that the major drive against viral infection remains defensive, based on the use of sound infection control principles and vaccination. Rigorous infection control policies have had significant impact in many situations, such as the transmission of hepatitis B virus (HBV) in renal dialysis units (UK Department of Health, 2002) and the spread of norovirus, the cause of winter vomiting disease, during outbreaks on hospital wards (Chadwick *et al*., 2000; McCall and Smithson, 2002). The eradication of smallpox and the elimination of poliovirus from large parts of the globe are two of the most striking examples of vaccine preventable disease, but there are many more, including the prevention of influenza virus infection (Nichol, 2003) and vaccination against HBV (Bonanni and Bonaccorsi, 2001).

There remain a limited number of antivirals, though in recent years there has been an explosive increase in licensed drugs. Nowhere is this more obvious than in the development of antiretroviral therapies for the treatment of HIV, with new drugs being licensed every year and many more entering clinical trials (Gulick, 2003). Not only are more antiviral compounds being developed and licensed, but there are also an ever-increasing number of situations where their use is being considered.

Antivirals are generally targeted at a single virus or closely related viruses, rather than a large group of viruses. Amantadine acts well against influenza A virus but has no activity against influenza B virus, and aciclovir is useful against HSV and varicella zoster virus (VZV), but is not effective as treatment for cytomegalovirus (CMV) or Epstein–Barr virus infections, despite these being members of the herpes virus family. There are two available antivirals that could reasonably be described as broad-spectrum: ribavirin (Snell, 2001) and cidofovir (Safrin *et al*., 1997). However, as their use is limited in many situations by uncertain *in vivo* efficacy and, for the latter especially, a poor safety profile, it is not possible to treat a presumed viral infection empirically.

A specific virus must either be suspected clinically or found to be present on diagnostic testing before antiviral treatment can be considered.

Examples of the currently available antivirals are detailed in Table 1. The majority of antiviral compounds in common current use are against viruses of

Table 1. Examples of currently available antivirals (British National Formulary, 2003; USA Food and Drug Administration, 2003)

Virus	Available antivirals	Main target (Molecular)	Resistance documented
HSV	Aciclovir, penciclovir, valaciclovir[a], famciclovir[a], foscarnet, cidofovir	Viral polymerase	Yes[b]
VZV	Aciclovir, valaciclovir[a], famciclovir[a], foscarnet	Viral polymerase	Yes[c]
CMV	Ganciclovir, valganciclovir[a], foscarnet	Viral polymerase	Yes[d]
Influenza A	Amantadine	Viral fusion protein	Yes[e]
	Zanamivir, oseltamivir	Viral neuraminidase	Yes[f]
Influenza B	Zanamivir, oseltamivir	Viral neuraminidase	Yes[f]
RSV	Ribavirin	Various modes of action	Not yet[g]
HBV	Lamivudine	Viral polymerase	Yes[h]
	Adefovir	Viral polymerase	Not yet[i]
	Interferon	Immune system and direct antiviral effects	
HCV	Ribavirin and interferon/pegylated interferon	Immune system and direct antiviral effects	Yes[j]
HIV 1	Abacavir, didanosine, lamivudine, stavudine, tenofovir disoproxil zalcitabine, zidovudine	Viral reverse transcriptase	Yes[k]
	Efavirenz, nevirapine	Viral reverse transcriptase	Yes[k]
	Amprenivir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir	Viral protease	Yes[k]

[a]Famciclovir, valaciclovir, and valganciclovir are prodrugs of penciclovir, aciclovir, and ganciclovir, respectively, with higher oral bioavailability.
[b]Morfin and Thouvenot (2003).
[c]Boivin *et al*. (1994).
[d]Limaye *et al*. (2000).
[e]Hayden and Hay (1992).
[f]Gubareva *et al*. (1998, 2001).
[g]Snell (2001).
[h]Dienstag *et al*. (1999).
[i]Marcellin *et al*. (2003).
[j]Pawlotsky (2000).
[k]Pillay *et al*. (2000).

the herpes family (HSV, VZV, CMV), influenza, and HIV 1. The majority are nucleoside analogues which inhibit viral polymerases including reverse transcriptase. Other targets include the influenza neuraminidase and HIV protease. There is currently a great deal of interest in the development of drugs with novel targets, such as the cellular virus receptor; such an approach may help to overcome the problem of cross-resistance between drugs with a similar mode of action.

As the number of antiviral drugs grows, and in particular their increased long-term use in chronic infections such as HBV and HIV, so the problems of resistance and toxicity become more marked and more challenging.

2. PROBLEMS ASSOCIATED WITH ANTIVIRAL THERAPY

2.1. Limited experience in antiviral use generally and locally

The majority of antivirals have been available for a relatively short time, such that there is little experience of their use in a range of conditions. Controlled clinical trials have generally been conducted only for one or two major indications. For example, valganciclovir was originally licensed only for CMV retinitis in AIDS patients, but as an oral preparation with equivalent activity to intravenous ganciclovir (Pescovitz *et al*., 2000), it had obvious advantages in the treatment and prophylaxis of CMV in transplant patients. In addition, trials tend to be carried out in selected populations of patients, which do not necessarily reflect everyday practise, where patients are more heterogeneous, and may differ in terms of coexisting pathologies and degree of adherence to treatment regimes. Experience with the drug therefore still requires to be built up both formally, with further published studies, and at a local level. This is a continuing process as use is expanded to more clinical situations and particular patient groups.

Limited information on a drug often means that it is considered as treatment in some situations where there is no evidence or consensus regarding efficacy. This is an issue particularly in severe life-threatening infections in the immunocompromised, where antivirals are used despite unproven clinical benefit. The use of drugs in these situations should be carefully monitored, and where possible included as part of larger studies.

As data on the use of a particular antiviral becomes available, it is important that information is disseminated to ward level and actual patient treatment.

2.2. Adverse effects

As viruses use host cell machinery for replication, enzymes such as the viral polymerase have significant homology to the cellular enzyme, thus resulting in an increased potential for inhibition of host cell processes. Many antivirals have a significant side-effect profile, for example, discontinuation of cidofovir is required in 25–30% of patients due to nephrotoxicity (Safrin *et al*., 1997). Other drugs, such as aciclovir and its derivatives, are relatively free of side effects, in part because they have a requirement for the viral thymidine kinase, and thus will only be metabolised to their active form in an infected cell. The likelihood and range of unwanted effects becomes much greater when treatment is required long term, and where combinations of drugs are used, such as in HIV. In these cases there is also a particular concern that the experience of side effects may effect adherence and thus have further adverse impact on the success of treatment.

2.3. Resistance

Antiviral drug resistance, due to mutation, has been described for almost all antiviral compounds (Table 1). Mutation is a common event for viruses, due to rapid replication rates. RNA-dependant RNA polymerases and reverse transcriptases are particularly error prone and lack the proofreading ability of DNA polymerases, thus mutation is particularly common in RNA viruses, such as HIV and influenza. Indeed RNA viruses are often described as existing as a quasispecies due to the vast variation which can exist in viral sequence, even within a single infected individual (Holland *et al*., 1992). Mutations resulting in antiviral drug resistance may arise during treatment with a particular drug, or may pre-exist within the viral quasispecies. In either case drug treatment selects out resistant virus and allows it to dominate. A pre-requisite therefore, for the emergence of resistant virus, is replication of the virus in the presence of the drug. This can be prevented by fully suppressing viral replication, though this is seldom achieved. The avoidance of subtherapeutic drug treatment is vital, as this can significantly increase the risk of resistance (Pillay and Zambon, 1998).

Resistance may take the form of single or multiple point mutations or deletions. These usually occur in sequences either coding for the target enzyme, such as the HIV reverse transcriptase, or for proteins necessary for drug activation, such as the HSV thymidine kinase. There are often a variety of mutations which can confer resistance to a particular drug—for example, both viral polymerase and thymidine kinase mutations can confer aciclovir resistance in HSV infection (Morfin and Thouvenot, 2003). The effect of a given mutation is not

always straightforward and there may be variation in the degree of resistance conferred. Unsurprisingly, where many drugs have the same viral target, cross-resistance to related antivirals is a common phenomenon. Some mutations confer resistance to one drug while increasing viral susceptibility to another, as with the M184V lamivudine resistance mutation in HIV reverse transcriptase, which increases viral susceptibility to zidovudine (Pillay *et al*., 2000).

There is great variation in the frequency with which resistance to a particular antiviral is observed and in the speed with which it emerges in a given treated patient. Amantadine treatment results in the emergence of resistant influenza in 30% of immunocompetent individuals within 5 days (Hayden and Hay, 1992), while to date virus resistant to the influenza neuraminidase inhibitor zanamivir has only been encountered rarely in immune compromised patients after prolonged treatment (Gubareva *et al*., 1998). In the treatment of HIV infection, resistance can arise rapidly to the non-nucleoside reverse transcriptase inhibitors such as nevirapine; in contrast, the development of resistance to the protease inhibitors is a slower process, requiring the accumulation of a number of different mutations (Pillay *et al*., 2000).

Antiviral drug resistance is a substantial problem in the immunocompromised and in long-term treatment regimes; these are the two areas where effective treatment is arguably most important. Two commonly encountered viral pathogens in transplant patients are HSV and CMV. Aciclovir resistance in HSV is common in these patients with up to 5% of viral isolates carrying resistance mutations (Morfin and Thouvenot, 2003). Although such viruses are attenuated in animal models, they can cause severe clinical disease in the immunosuppressed. In opportunistic CMV disease, resistance to the front-line antiviral ganciclovir can be observed in association with prolonged drug exposure, such as during prophylactic regimes (Limaye *et al*., 2000). In chronic HBV, up to a third of patients show resistance after 1 year's treatment with the nucleoside analogue lamivudine (Dienstag *et al*., 1999). Antiretroviral regimes, which are potentially life-long, with three or more drugs give ample time for resistance mutations to emerge, often to more than one drug (Pillay *et al*., 2000). Given that a particular viral mutation can confer resistance to several related antiretrovirals, the available effective antivirals can rapidly become limited, particularly after two or three changes in therapy. Resistance is one of the main driving forces in the continuing search for new drugs against HIV.

Resistance is not a common problem in the treatment of most acute infections such as genital herpes simplex, or varicella zoster in immune-competent individuals. This may be explained by the fact that mutant viruses are often attenuated with respect to the wild-type virus and less fit with regard to their replication competency (Nijhuis *et al*., 2001). Unfit, resistant virus may therefore be more easily dealt with by an intact immune system. In addition, mutations can take some time to emerge, often longer than the time required to complete a course of treatment for an acute infection.

From the public health perspective, a concern is the risk of spread of resistant virus. Resistant viruses are not yet commonly found circulating in the community, perhaps, as lacking selective pressure from an antiviral, the fitter wild-type forms predominate. Whether this situation will change as antiviral use increases is currently unclear. There are, however, many examples of the transmission of resistant viruses between individuals. In particular there is mounting concern regarding the increase in transmission of resistant HIV in western countries since antiretroviral therapy became widely available, including the transmission of multiply drug resistant virus (UK collaborative group on monitoring the transmission of HIV drug resistance, 2001). Another example is the anti-influenza drug amantadine, which is one case where resistant virus commonly emerges in immune competent individuals, the resistant influenza is readily transmitted and spread of resistant virus has been observed during outbreaks (Hayden and Hay, 1992).

As antiviral use increases, it is inevitable that resistance will be encountered more commonly, both in the individual patient undergoing treatment and in the wider community. This again emphasises the need for rational drug use, particularly with a view to preventing the emergence of resistant virus.

3. ANTIVIRAL TREATMENT STRATEGIES

Antiviral policies must ensure that any treatment is indicated, and appropriate with regard to three major goals: successful treatment of the patient's illness, avoidance of treatment-related adverse effects, and prevention of the emergence of resistant virus.

3.1. Sources of information and advice

In a rapidly evolving field such as the treatment of viral disease, the evidence base changes as new antivirals are developed and more studies are completed on existing drugs. National guidelines, produced by professional bodies, are evidence-based recommendations, which are supplemented by expert opinion where necessary. Examples in the United Kingdom include: The British HIV Association (BHIVA) guidelines giving the most recent recommendations for HIV treatment (BHIVA, 2003); The Royal College of Obstetrics and Gynaecology guidelines, which are regularly reviewed and cover the treatment of genital HSV and VZV in pregnancy (RCOG, 2001, 2002); and government associated agency guidance, such as the UK National Institute of Clinical Excellence recommendations covering Influenza (NICE, 2003). In the United States guidelines on a number of virology issues are published by the Centers for Disease Control and Prevention (e.g., Bridges *et al*., 2003; Dybul *et al*., 2002). Similar guidelines are available from national bodies

in other countries. National guidelines can be adapted to local protocols taking into account local factors such as referral routes, prescribing policies, and the available viral diagnostic and monitoring services. Guidance on the use and monitoring of antiviral treatment is also available from a number of recent reviews (Pillay *et al*., 2002; Waugh *et al*., 2002). Guidelines may not exist for situations where there is little information or no clear evidence of efficacy, or where there are conflicting studies, such as ribavirin for parainfluenza virus infections in the immunocompromised (Elizaga *et al*., 2001) or cidofovir in progressive multifocal leukoencephalopathy (Segarra-Newnham and Vodolo, 2001).

3.2. Confirm the diagnosis

Good laboratory virology provision is essential to the use of antiviral agents. As antivirals tend to have a limited spectrum of activity and are often associated with significant toxicity and cost, it is important to confirm a suspected diagnosis. Ideally this would be done prior to commencing treatment, although sometimes this may not be possible. Examples of this are where delay might have serious consequences, as in suspected HSV encephalitis, or where early treatment (within 36 hr of onset of disease) is required for therapeutic benefit, as in influenza virus infection. In such cases it is still important that laboratory confirmation is obtained as soon as possible, to ensure the correct treatment or allow cessation of unnecessary treatment. In the past diagnosis was often retrospective, requiring several days or even weeks for virus growth in tissue culture or entailing the testing of convalescent blood samples. Some viruses cannot be grown in standard cultures and sensitivity is often too low to reliably detect low amounts of virus (as with cerebrospinal fluid (CSF) in HSV encephalitis). The arrival of the polymerase chain reaction (PCR) in laboratories has revolutionised the impact of diagnostic virology in clinical practice (Carman, 2001). This technique is a highly sensitive and specific method for the detection of viral nucleic acid, and can be adapted to detect practically any virus in any body fluid or tissue. With classical PCR a result can generally be available within 1–2 days, however the recent advance to real time PCR allows a result to be available within a few hours (Niesters, 2002). This means that in many cases it is possible to await a confirmed diagnosis before starting treatment. Such rapid techniques are particularly useful in serious illnesses where the cause of symptoms cannot be satisfactorily determined clinically, for example, systemic illness in a transplant recipient which could be due to a number of factors including potentially treatable viral infections such as CMV or adenovirus, or where the side effects of unnecessary treatment could compromise other aspects of patient management as with increased neutropoenia with ganciclovir in bone-marrow transplant patients. In all cases adequate

samples, usually from the site of infection, should be taken as soon as possible. Where there is any doubt as to the correct sample, sample collection buffer, or method of sample transport, the laboratory should be consulted.

3.3. Limit antiviral use where possible

In the majority of patients most viral infections do not require treatment. This will limit adverse effects and selection of resistant virus. For example, although aciclovir is an effective treatment for primary varicella zoster infection (chickenpox), there is little benefit in treating children with uncomplicated infection, as the illness is generally self-limiting with serious complications being rare (Tarlow and Walters, 1998). Similarly, although the drug pleconaril has recently been shown to reduce the severity of rhinovirus infections (Hayden *et al*., 2003), its use is not currently indicated in upper respiratory tract infections in otherwise healthy patients. It is also important not to use antivirals in situations where they have been shown not to be of benefit. Thus, although aciclovir can inhibit Epstein–Barr virus replication in vitro, it has not been shown to be effective in cases of glandular fever, probably due to the immune-mediated nature of the illness (van der Horst *et al*., 1991).

3.4. Correct timing of treatment

It is important to start treatment at the optimum time. For acute infections, most antivirals are only effective if commenced rapidly. In adults with primary varicella zoster, treatment is normally only recommended if it can commence within 24 hr of rash onset, or within 36–48 hr of symptom onset in influenza virus infection, as there is little evidence of efficacy beyond this point (Couch, 2000; Wilkins *et al*., 1998) and viral replication has usually peaked. This requires systems to be in place to see, diagnose, and treat such patients quickly. In many situations treatment may need to be started on a clinical basis unless very rapid PCR (or direct immunofluorescence) results can be obtained. Unnecessary treatment can be discontinued if the original diagnosis is not confirmed. In the case of recurrences of genital herpes, patients are often provided with antivirals in advance so that they can commence treatment at the first sign of symptoms (Drake *et al*., 2000).

In chronic illness, factors indicating a need for antiviral treatment are not always present at diagnosis and very often treatment may be not be required for several years, if at all. Delaying treatment prolongs the development of resistance. Thus, in chronic HBV or HCV infection treatment is not normally indicated until liver biopsy, among other factors, shows a certain degree of pathology (Booth *et al*., 2001; Wai and Lok, 2002). The high incidence of

HBV resistance to lamivudine means that earlier treatment may reduce the value of the drug when liver pathology reaches the stage where treatment really is indicated. In the case of HIV, once treatment is started it requires to be carried on life-long; this has major implications in terms of chronic debilitating side effects such as lipodystrophy (Bodasing and Fox, 2003) and the emergence of viral resistance. The latter necessitates changes in treatment regime that can rapidly reduce the antiviral options available to the patient in the future.

3.5. Correct drug choice

Having decided that antiviral treatment should be commenced, the next step is to decide on the correct drug, or drug combination. Despite the relatively limited number of antivirals, there are a number of options for most treatable viral infections (see examples in Table 1, or for more detailed information see Waugh *et al*., 2002). The decision will be based on a number of factors: efficacy, side-effect profile, route of administration, dosage schedule, resistance profile of the drug and the virus, underlying pathology, and cost.

Proven efficacy. Where possible a drug should be chosen in line with evidence-based guidelines or controlled trial data for that particular situation.

Side effect profile. Where alternatives exist an antiviral should be chosen which has the fewest side effects. Thus in the treatment of HSV, foscarnet, which is an effective inhibitor of viral replication, is not the first-line treatment due to a poor safety profile with nephrotoxicity (Balfour *et al*., 1994).

Route of administration. Many antiviral compounds that are currently available are formulated for only one route of administration, it is therefore important to attempt to use one which can be delivered in a way which ensures adequate drug levels and maximises the likelihood of adherence. Inhalers are often difficult for elderly patients to administer correctly, thus for an elderly patient with influenza, the oral neuraminidase inhibitor oseltamivir may be preferred to inhaled zanamivir (Diggory *et al*., 2001).

Dosage schedule. If adherence is likely to be a problem, or treatment will be long term or frequent, then an antiviral requiring fewer daily doses may be preferred. In the treatment of recurrent genital herpes simplex infection the oral aciclovir dose is five times a day while valaciclovir requires administration only twice daily (British National Formulary, 2003). In HIV treatment regimes multiple factors need to be considered, such as the dosage interval of the different drugs in the regime, whether or not food should be taken at the same time, and in the patient's own daily routine. Fitting the regime as much as possible to the patient's lifestyle helps improve tolerability and thus adherence (Trotta *et al*., 2002).

Resistance profile of the drug. In some situations it is particularly desirable to use an antiviral that is less prone to selecting out resistant virus. In nursing homes, for example, a neuraminidase inhibitor may be preferred to amantadine for the treatment of influenza, as the rapid emergence of resistance to the later would result in the spread of resistant virus (Hayden and Hay, 1992). Where the patient is known to have a virus resistant to a particular antiviral, a drug should be used where cross-resistance is unlikely to be a problem.

Underlying patient pathology. The relative importance of a particular side effect will often vary when the patient has other coexisting pathology. Hence, although ganciclovir is normally the first-line choice in CMV infection in the immunocompromised, in patients where myelosuppression is a particular concern, foscarnet may be preferred, despite its nephrotoxicity, as it causes less neutropoenia.

Cost. Antiviral cost is an issue that can never be overlooked. The newer drugs tend to be more expensive than those that are more established. Where two equally effective alternatives exist the cheaper should always be considered. However, a number of factors need to be considered, such as the likelihood of adherence and possible side effects, and the cheapest drug will not necessarily be the most cost-effective in overall terms.

3.6. Correct dose and duration

Achieving an antiviral dose sufficient to maximally suppress viral replication is critical not only in terms of successful treatment of the infection, but also to prevent the development of resistant virus. Subtherapeutic antiviral doses result in viral replication in the presence of a drug, thus allowing the emergence of resistant virus. General recommendations on antiviral doses are available from national and local formularies, but a number of factors need to be considered before deciding on a dose for a patient in a particular situation. One factor is the susceptibility of the virus to the antiviral. The IC_{50} for aciclovir (the concentration required to inhibit viral replication by 50%) is 10-fold greater for VZV than for HSV. The latter therefore requires higher treatment doses. A further factor is the site of the infection and the ease with which the drug can penetrate that compartment of the body. Only 50% of intravenous aciclovir serum concentrations are achieved in the CSF, so again higher doses are recommended for HSV encephalitis.

In acute illness the aim is normally to continue treatment until the viral infection is resolved by a combination of the antiviral and the patient's own immune system. Where the immune system is not acting optimally this often results in a requirement for longer duration of treatment. In chronic infection, where the aim

is to control rather than cure the disease, treatment may be continued indefinitely if benefit is still being achieved. In HBV infection lamivudine is often continued for several years, and in HIV treatment it is usually expected to continue life-long once started. This can lead to resistance if treatment is stopped, particularly for drugs with a long half-life, as there is an effective period of under-treatment as antiviral levels drop, so replication continues in the presence of suboptimal drug concentrations. Nevertheless, stopping treatment may be necessary due to side effects or if patient wishes. If possible a replacement regime should be instituted immediately to suppress replication. A controversial therapeutic strategy for HIV, known as a structured drug interruption (Gulick, 2002), is aimed at boosting the patient's own immune response to the virus and allowing them a break from arduous treatment regimes. Although there are potential benefits, one of the major concerns is the risk of promoting the emergence of resistant virus.

3.7. Adherence

As with all medical treatment the adherence of the patient to the regime is vital to its success. Erratic drug intake results in subtherapeutic drug levels with treatment failure and resistance. In patients on short-term courses of antivirals for acute infections, such as primary herpes simplex, this is less of a concern. In HCV the patients require to undergo treatment with a combination of interferon and ribavirin for 6 months or more. The interferon is given by subcutaneous injection and most patients experience flu-like illness and lethargy, with a significant percentage suffering depressive symptoms. Especially as the patient may not have felt particularly unwell prior to treatment, the future benefits may be less obvious to them than the acute side effects. In HIV, regimes are complex with multiple drugs and significant side effects, particularly given the long-term nature of treatment. Adherence may be compromised by all these factors. It is important that regimes are kept as simple as possible and that patients are fully informed regarding their treatment and the need for good adherence.

3.8. Combination antiviral therapy

Combination treatments, which can prevent or delay the development of resistance, are most commonly used for chronic conditions. In HCV, the combination of interferon and ribavirin helps achieve viral suppression by a combination of boosting host immune responses and direct viral effects. In HIV combination therapy with three or more antiretrovirals from two or three classes of drug (Highly Active Antiretroviral Therapy—HAART) has resulted in regimes of sufficient potency to fully suppress viral replication, which should delay the emergence of resistant virus. There are, however, also obvious

disadvantages, with cumulative side effects and drug interactions. Adherence to combination regimes has been greatly helped by the availability of antivirals as compound preparations containing two or three drugs, which reduces pill burden and improves compliance. As with all compound drugs, this does limit the flexibility to change individual drugs and their doses.

3.9. Monitoring treatment

Often, simple clinical improvement is all that is required to monitor antiviral treatment, for example, in acute infection with influenza or herpes simplex in the immunocompetent. For chronic infections, or infections in the immunosuppressed, regular testing is required. This may be qualitative, for example, weekly testing after infection or reactivation of CMV, or quantitative, such as in HBV and HIV infections (Pillay *et al*., 2002).

Where symptoms fail to resolve or worsen on treatment, or where laboratory testing shows a failure to suppress viral levels or viral rebound, the antiviral regime should be reviewed in terms of dose, duration, and adherence, and other possible confounding patient factors considered. If, despite optimised treatment, symptoms still fail to resolve, resistance should be considered (Pillay *et al*., 2002). Viral resistance testing is now usually based on sequencing of the virus and identification of known resistance mutations, rather than on viral susceptibility in culture. This is generic technology and is becoming increasingly available in regional virus laboratories. The detection of resistant virus normally indicates the need to change therapy.

Monitoring is particularly important where an antiviral is being used in a situation where experience and evidence for benefit is limited. In such cases both regular clinical and virological review are essential.

4. ANTIVIRAL PROPHYLAXIS STRATEGIES

Many of the considerations above for the use of antivirals in the treatment of viral infections are also relevant when considering the use of antivirals for prevention. One should consider in which situations antiviral prophylaxis is warranted, and whether there are alternatives, such as vaccination or pre-emptive treatment strategies for CMV.

Prophylaxis should only be considered where there is a significant risk of a specific viral infection or of reactivation, where such infection would cause a significant risk to the patient and where effective vaccination is not possible. The need for prophylaxis must also be balanced against the possible disadvantages, such as unwanted side effects and possible selection for resistance.

4.1. Restrict to necessary situations

Most routine antiviral prophylaxis is used in patients on immunosuppressive regimes, usually post-transplant, and patients with low CD4 counts in HIV infection. The aim is to prevent primary infection or reactivation of latent infection. The main viral targets are CMV and HSV. Not all immunocompromised patients require prophylaxis, and protocols should define those patients for whom it is necessary. The decision should be based on the likelihood of infection or reactivation and the severity of the immunosuppressive regime or level of the CD4 count. In solid-organ transplants, CMV prophylaxis is often only considered where there is a miss-match in serostatus, such that a primary CMV infection will result from transplant of an organ from a seropositive donor. In HIV, CMV reactivation and disease become a problem requiring prophylaxis only when CD4 counts fall below 50 (Kaplan *et al*., 2002).

Antiviral prophylaxis can also be used to prevent infection post-exposure, such as after significant contact with HIV (Department of Health, 2000). It is important to reserve treatment to situations where there is a real risk of infection, especially for HIV where treatment requires multiple drugs and side effects are common. Thus, a needlestick requires a thorough risk assessment to establish whether significant blood contact occurred and the likely HIV status of the source.

Prophylaxis may also be indicated to prevent spread of infection in outbreaks. Again it should only be considered in high-risk situations, such as an influenza outbreak in a nursing home with elderly patients, or in a hospital ward with immunocompromised patients. As described below vaccination is normally the preferred option in these situations.

4.2. Alternatives to antiviral prophylaxis

It is always important to consider alternatives to drug therapy. Two options are vaccination and pre-emptive treatment strategies.

Vaccines, where available, are the preferred method for viral prophylaxis pre-exposure and often also post-exposure, for example, the hepatitis B vaccine and influenza vaccines (Department of Health, 1996). Vaccine, or a course of vaccine, need usually only be given once in a lifetime or, in the case of influenza, yearly. They generally have minimal side effects and no further action is required if contact does occur. Antiviral prophylaxis may still be required in some circumstances where a vaccine is available, such as where vaccine is contraindicated or response to vaccination is poor, as in the immunocompromised. Passive vaccination with immunoglobulin may be another option after contact. For example, varicella zoster immunoglobulin is available after

contact with VZV and is usually preferred to aciclovir as there is more information on its use in this situation (Department of Health, 1996).

In some transplant units a CMV pre-emptive strategy is used in place of antiviral prophylaxis. In this situation patients at risk of CMV infection or reactivation are monitored by PCR at regular intervals (usually once or twice a week). When the virus is detected in the blood, or levels are seen to be rising in quantitative assays, antiviral drug is started at treatment, rather than prophylaxis, doses. This has the advantage of limiting drug treatment, thus minimising side effects and reducing the emergence of resistant virus. There is still debate on which strategy is best (Emery, 2001; Hart and Paya, 2001). It should be noted that for pre-emptive strategies to succeed there needs to be adequate laboratory funding and expertise and a high degree of organisation regarding the collection, transport, and testing of samples and communication of results.

4.3. Timing and duration of treatment

Ideally a patient should be on prophylaxis before there is significant risk of infection or reactivation. Thus treatment should start before or soon after transplant, or when the CD4 count is seen to be dropping towards the threshold for treatment in HIV. Treatment should continue until immunity is reconstituted to a significant level, often taken as 100 days post-transplant. Various studies have shown that although immune reconstitution on HAART in HIV is not necessarily complete it appears to be safe to discontinue prophylactic treatment when the CD4 count has risen (Macdonald *et al*., 1998).

Timing of treatment is vital for post-exposure prophylaxis. For example, after a significant needlestick from an HIV positive source, antiretroviral post-exposure prophylaxis should ideally start within 1 hr of contact (Department of Health, 2000). In contrast, following contact with VZV in a high-risk individual, such as a pregnant woman, aciclovir treatment is given from 6 to 10 days post-contact in keeping with the natural history of the infection and timing of viraemia (Asano *et al*., 1993).

4.4. Drug choice and dose

Drug choice should be guided by the factors mentioned in the discussion on treatment strategies. Avoidance of side effects is particularly important given the fact that the patients are not being treated for an active infection. Drug doses for prophylaxis are often lower than those recommended for treatment. Drug choice is a particular issue for post-exposure prophylaxis in HIV, where knowledge of the source's treatment history, and possible viral resistance profile, may influence the treatment combination chosen.

4.5. Adherence

Adherence is important for successful antiviral prophylaxis. It is important that the patient is aware of the reasons why the treatment is necessary.

4.6. Monitoring for infection

Prophylactic regimes do fail. Prophylaxis doses are generally lower than those required for effective treatment, thus it is necessary to react quickly to the development of infection, not only to ensure correct treatment, but also to prevent the development of resistance on regimes that are not fully suppressive. Clinical and virological monitoring is important. Where monitoring detects active viral infection or a patient becomes unwell on prophylaxis, samples should be taken to confirm the diagnosis as quickly as possible, although it may be necessary to start treatment before results are available.

5. CONCLUSION

Antiviral therapy continues to be a rapidly expanding field. Complex issues need to be addressed such as the effects of long-term use and the emergence of resistance. If these agents are to realise their full potential both now and in the future it is essential for their use to be the subject of rational and well monitored prescribing practises.

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