Antivirals in the context of HIV disease

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Antiviral drugs, other than those with anti-retroviral activity, are used in persons with human immunodeficiency virus (HIV) infection for two purposes: treatment or prevention of viral infections that cause disease in persons with immunodeficiency, and to suppress viruses that might act as co-factors and promote replication of HIV itself. Human herpesviruses are the major targets of therapy in both settings. The herpesviruses, particularly cytomegalovirus (CMV), herpes simplex virus (HSV) and varicella-zoster virus (VZV) act as opportunistic pathogens as cell-mediated immunity declines, and there is theoretical, in-vitro, and in-vivo evidence that one or more herpesviruses can accelerate the progression of HIV disease. Therapy and prophylaxis with antiviral compounds such as acyclovir, ganciclovir and foscarnet are well established in HIV infection, and this article will review their present use and recent improvements in formulations and drug delivery.

Introduction

Antiviral therapy in persons infected with a human immunodeficiency virus (HIV) may be used either to prevent or treat a viral infection that causes clinical illness, or as a means of suppressing replication of a virus that promotes the replication of HIV itself and hence accelerates immunodeficiency, the development of AIDS and, ultimately, death. Such therapy is almost exclusively directed against herpesviruses, since these are not only a prominent cause of opportunistic infections but are also the major candidate viruses for a role as co-factors in HIV replication.

All human herpesviruses (Table I) have a very high prevalence worldwide but, in immunocompetent individuals, rarely cause mortality. They characteristically cause primary infection, often early in childhood, followed by a period of latency and, perhaps, reactivation to cause relatively minor illnesses. In the host with latent herpes virus infection, cellular immunity is important in modifying the pathogenicity of the virus and control of symptomatic recurrences. Following acquisition of HIV, there is a consequent decline in immune system function and the patient becomes increasingly susceptible to a number of viral, bacterial, fungal and protozoal infections. Herpesviruses among the viral agents are important and individuals with HIV infection are much more likely than others to suffer clinical reactivation of their latent herpesviruses. Furthermore, immunocompromised patients, particularly those with advanced HIV and AIDS, are prone to much more severe and progressive herpesvirus
Table I. Human herpesviruses

| Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) |
| Varicella-zoster virus (VZV) |
| Cytomegalovirus (CMV) |
| Epstein-Barr virus (EBV) |
| Human herpesvirus 6 (HHV-6) |
| Human herpesvirus 7 (HHV-7) |
| Human herpesvirus 8 (HHV-8) |

infections, and such infections are, indeed, the leading viral cause of morbidity and mortality in individuals with AIDS (Hoover et al., 1993). The frequency and severity of herpesvirus infections in individuals with HIV makes the use of prophylaxis and prompt therapy with appropriate antiviral therapy an important consideration.

Herpes simplex virus

Although the prevalence varies in different populations, most adults infected with HIV will also have serological evidence of prior infection with herpes simplex virus (HSV) (Nerurkar et al., 1987). Clinical recurrence of such infection, particularly genital herpes, not only causes significant morbidity in HIV-positive individuals but epidemiological studies have shown that genital ulcer disease (of which HSV is the commonest cause in industrialized nations) is an important risk factor for the acquisition of HIV infection (Wasserheit, 1992; Telzak et al., 1993).

As in immunocompetent individuals, the spectrum of HSV disease in HIV-infected persons is wide (Table II), although oral and genital infections cause the major problems. The site of HSV infection differs between the risk groups to which the HIV-infected individual belongs: children suffer primary and recurrent oropharyngeal herpes, homosexual men have a high rate of peri-anal and rectal herpes and, in intravenous drug users, peri-oral and genital lesions are more common. HSV ulcers are painful and, in HIV-positive persons with CD4 cell counts below 100/mm$^3$, can involve wide areas of skin and be very prolonged and debilitating (Drew, Buhles & Erlich, 1992). The destruction of mucosal and skin integrity resulting from HSV ulceration predisposes the individual to acquisition of bacterial and fungal superinfections, and chronic herpes labialis or HSV oesophagitis may compromise nutrition and contribute to the weight loss of HIV disease. Mucocutaneous HSV that persists for longer than one month is an AIDS-defining illness.

Although recurrent HSV infections are not prognostic markers in HIV-positive persons, recognition of their impact on quality of life should prompt early therapeutic intervention, either on an episodic or a continuous, suppressive basis. Acyclovir is the

Table II. Spectrum of HSV disease seen in HIV-positive persons

| Peri-oral/facial infection | Whitlow |
| Oesophagitis | Genital herpes |
| Peri-anal/rectal infection | Disseminated disease |
| Keratitis | Acute necrotizing retinitis |
| Encephalitis | Aseptic meningitis |
antiviral drug that is routinely used for the management of HSV infections in patients co-infected with HIV, and the optimum dose and route of administration depend on the severity of immunosuppression and the site and severity of the lesions. In early HIV infection, oral therapy at a dose of 200 mg five times daily until all the lesions have crusted is often suitable for primary or recurrent mucocutaneous disease (Shepp et al., 1985), although this dose may be doubled in patients with more advanced HIV disease or those with impaired gastrointestinal absorption (Drew et al., 1992).

For the patient with frequent recurrences of HSV infection (especially genital or rectal herpes), suppressive therapy with acyclovir may be more convenient, reduce the risk of secondary fungal and bacterial infection of mucosal breaches, and may confer survival advantages, as discussed below (see Section on co-factors). For effective suppression of clinical disease, a dose of 800 mg/day acyclovir is usually needed (Mindel et al., 1988). This may be given as either 200 mg qds or, probably more conveniently for most patients, as 400 mg bd. Such suppression has been continued safely for several years in immunocompetent patients (Goldberg et al., 1993), although recurrences usually develop within a few months of discontinuing of therapy. Breakthrough recurrences that develop while the patient is taking suppressive acyclovir may be treated by increasing the dose.

In patients with particularly severe or extensive mucocutaneous HSV infection, or in those with visceral dissemination or herpes encephalitis, iv acyclovir (5–10 mg/kg or 500 mg/m² every 8 h) should be used and continued for at least 10 days.

Acyclovir-resistant strains of HSV have been estimated to cause 4% to 5% of infections in immunocompromised hosts (Englund et al., 1990), but the exact incidence in AIDS patients is unknown. They have been isolated most frequently from perirectal sites in HIV-positive men treated with long-term acyclovir (Erlich et al., 1989; Chatis & Crumpacker, 1992; Katz, Rosenblat & Pisanty, 1992; Collins & Ellis, 1993). Such strains are usually thymidine kinase deficient (TK-negative) mutants. Since, unlike acyclovir and ganciclovir, foscarnet does not require viral TK-mediated phosphorylation for activity, TK-negative strains of HSV can be treated successfully with iv foscarnet therapy, 40 mg/kg every 8 h (Birch et al., 1990; Stellbrink et al., 1991; Hardy, 1992). A comparative study showed that such therapy was superior to the use of vidarabine (Safrin et al., 1991). Subsequent recurrences at the same site are often due to acyclovir-sensitive virus since TK-negative mutants seem less capable of establishing latency; they are also, therefore, less likely than sensitive virus to be transmitted and cause infection in sexual partners. They are of reduced virulence in some animals but appear to be capable of causing severe clinical disease in humans (Marks et al., 1989; Englund et al., 1990).

Very rarely, acyclovir-resistance in HSV is caused by mutation in the DNA polymerase and such strains may also be resistant to foscarnet (Birch et al., 1990; Chatis & Crumpacker, 1992). Topical cidofovir (hydroxy-[phosphonylmethoxy] propylcytosine, HPMPC) has been used to treat several such cases (Snoeck et al., 1994a). Cidofovir is a nucleotide (rather than the more common nucleoside) analogue and hence bypasses the initial virus-dependent phosphorylation. Cellular enzymes convert cidofovir into the active diphosphate metabolite and the drug has prolonged antiviral activity against several herpesviruses, including HSV and cytomegalovirus (CMV) (De Clercq, 1993).

HSV infections that persist despite oral acyclovir therapy should not automatically be assumed to be caused by acyclovir-resistant strains. The possibility of poor compliance with treatment or failure of absorption due to gastrointestinal disease
should be considered and excluded. It is also important, before commencing foscarinet therapy for suspected acyclovir-resistance, to ensure that samples for virological culture and sensitivity testing are obtained.

**Varicella-zoster virus**

In Western countries, primary varicella-zoster virus (VZV) infections are rare in HIV-positive adults, since most will have been previously infected after exposure to VZV during childhood. Varicella is seen in HIV-infected children, however, and both children and adults with HIV infection often suffer reactivation of VZV to produce herpes zoster (Verroust, Lemay & Laurian, 1987). Other, atypical, manifestations of VZV reactivation also occur.

Studies of prospectively followed cohorts of HIV-infected children have shown that, in contrast to other populations of immunocompromised children, chickenpox is usually not significantly different from that in HIV-negative children: occasionally, severe cases do occur, particularly in children with AIDS (D. Gibb, personal communication). These cases may be more prolonged than usual, suffer visceral complications or recur as further varicella or herpes zoster (Jura et al., 1989; Patterson, Butler & Edwards, 1989; Leobovitz et al., 1993; Srugo et al., 1993; Kelley et al., 1994). Varicella-naive, HIV-infected, children exposed to chickenpox should be offered varicella zoster immunoglobulin (VZIG), although, as seen in the immunocompetent individual chickenpox still occurs sometimes despite such prophylactic measures (Srugo et al., 1993). The use of acyclovir, given during the incubation period in order to ameliorate the severity of VZV infection has not been studied in HIV-positive children, but was helpful in immunocompetent family contacts of a case of chickenpox (Asano et al., 1993).

The incidence of herpes zoster is much higher in HIV-positive patients compared with the general population. In the USA, for instance, the age-adjusted relative risk is 17 for HIV-positive compared with HIV-negative homosexual men, with a steady increase in the cumulative proportion developing herpes zoster in the decade following HIV seroconversion (Buchbinder et al., 1992). In Africa, there is a clear association between HIV seropositivity and herpes zoster (Dehne et al., 1992) and the annual incidence is seven-fold higher in HIV-infected individuals than in the general population of the USA (Friedman-Kien et al., 1986). There is no prognostic implication of herpes zoster in the HIV-infected individual (Buchbinder et al., 1992; Glesby, Moore & Chaisson, 1993).

The clinical severity of herpes zoster in individuals with HIV correlates with the degree of immune dysfunction. In the early stages of HIV infection, herpes zoster is a self-limiting infection, similar to that in otherwise healthy individuals. Patients with advanced HIV disease, however, are at risk of severe, prolonged, recurrent and atypical cutaneous manifestations and visceral dissemination to the lungs, liver and central nervous system (Cohen & Grossman, 1989).

Acute retinal necrosis due to VZV is a rare but sight-threatening manifestation that occurs in patients with very low CD4 cell counts (Jabs et al., 1989b; Wood, 1994). Other manifestations of VZV disease that occur, without necessarily any dermatological signs in patients with AIDS, include multifocal leukoencephalitis, meningomyeloradiculitis, vasculitis and cerebral infarction, and brain stem encephalitis (Cohen & Grossman, 1989; Moullignier et al., 1995).

When chickenpox occurs in HIV-infected individuals (both adults and children), therapy with acyclovir should be considered, although some children who develop
varicella early in the course of HIV infection recover uneventfully with no antiviral therapy (D. Gibb, personal communication). Oral acyclovir (800 mg or 20 mg/kg qds for adults and children, respectively) is probably appropriate for varicella in the asymptomatic stages of HIV infection and while immune function is adequate, but for those who develop primary VZV when they are severely immunocompromised, and for those with visceral involvement, iv acyclovir (10 mg/kg or 500 mg/m² every 8 h for 7–14 days) should be prescribed.

For most cases of herpes zoster in the HIV-infected patient a standard dose of acyclovir (800 mg five times daily) is sufficient, although therapy may need to be continued beyond the normal 7 days until the lesions have healed. Intravenous acyclovir can be reserved for more severely affected individuals or those with disseminated disease. The poor prognosis of VZV acute retinal necrosis or neurological disease, despite high-dose acyclovir, is possibly related to poor penetration of acyclovir across the blood-brain barrier.

Suppression of recurrences of herpes zoster with acyclovir is usually not undertaken intentionally, since episodes occur at long intervals. Even if such an approach were to be adopted (after three recurrences, perhaps) the optimal dose has not been determined, although herpes zoster is uncommon in patients receiving acyclovir at doses of 600–800 mg/day for other reasons (Cooper et al., 1993; Youle et al., 1994). Acyclovir-resistance in VZV has been reported in severely immunocompromised HIV-infected individuals who have been previously treated with long-term suppressive acyclovir for recurrent HSV or VZV infection (Jacobson et al., 1990; Snoeck et al., 1994b). Most such strains are sensitive to foscarnet and can be treated with iv foscarnet 120 mg/day in divided doses until the lesions have healed (Balfour et al., 1994). At present there are no rapid methods for determining VZV sensitivity to acyclovir and if herpes zoster were to develop in a patient receiving maintenance ganciclovir therapy for CMV disease then, after taking suitable specimens for viral culture, it would seem prudent to use foscarnet to treat both the herpes zoster and the CMV.

Cytomegalovirus

The seroprevalence of CMV is very high in most populations of HIV-infected adults. This is particularly so in homosexual men with AIDS, in whom the seropositivity is near to 100% (Schooley, 1990). Hence, most of the manifestations of CMV in adult patients co-infected with HIV probably result from viral reactivation. In HIV-positive children, however, primary CMV occurs and has a great impact, producing disseminated disease similar to that seen in organ transplant recipients (Tovo et al., 1992). CMV disease is particularly prevalent in patients with advanced HIV disease and is becoming more common with improved survival of AIDS patients (Hoover et al., 1993). Although only 30% or so of HIV-positive individuals develop symptoms due to CMV disease, autopsy studies show that the true prevalence of disease is nearly twice as high (Pillay et al., 1993). The commonest sites for symptomatic CMV disease are the retina and gastrointestinal tract but, at autopsy, neurological infections are seen most frequently.

In Western countries, CMV retinitis is the leading ocular infection in patients with AIDS, affecting some 20% to 30% of patients, almost invariably those with CD4 cell counts <50/mm³ (Jabs, Enger & Bartlett, 1989a; Hoover et al., 1993). CMV retinitis
is a clinical diagnosis, made by ophthalmological examination. It should be suspected even if ocular symptoms are subtle and non-specific, since it can be rapidly sight-threatening if untreated. It is rarely diagnosed in African patients with AIDS. This may reflect the shorter survival of AIDS patients in Africa or the frequency of CMV disease among HIV-positive homosexual men compared with other risk groups (Gallant et al., 1992). CMV infection of the gut may result in fever, pain, gastrointestinal bleeding, malabsorption and/or diarrhoea, and patients with CMV oesophagitis is apt to cause dysphagia (Schooley, 1990). Pulmonary and adrenal disease may also occur (Pillay et al., 1993) and a clear clinical entity of CMV encephalitis and dementia has now been described (Holland et al., 1994). The diagnosis of CMV disease can be very difficult since the presence of CMV does not necessarily indicate that it is the cause of symptoms. CMV viraemia is not predictive of the development of CMV disease but should be regarded as an indication for close observation and evaluation for its development and treatment (Zurlo et al., 1993).

At present the only drugs available for the treatment of CMV disease are ganciclovir and foscarnet (Dhillon, 1994); cidofovir (HPMPC) is unlicensed although under clinical trial. For retinitis, the aim of therapy is to stop further spread of retinal necrosis, although at autopsy almost all patients will have CMV disease elsewhere (Pepose et al., 1985). Intravenous ganciclovir or foscarnet, given as induction therapy for 2 to 3 weeks will delay the time to progression of CMV retinitis, but if treatment is stopped relapse is almost inevitable (Buhles et al., 1988; Jabs et al., 1989a; Palestine et al., 1991; Katlama et al., 1992). Hence, induction therapy with ganciclovir, 5 mg/kg 12-hourly, or foscarnet, 60 mg/kg 8-hourly or 90 mg/kg 12-hourly, needs to be followed by regular ophthalmological examinations and maintenance therapy with a lower dose of drug (ganciclovir 5 mg/kg or foscarnet 90 mg/kg for 5–7 days each week). Despite this, relapse is common and when detected the induction dosage must be recommenced. The usual response to re-induction argues against most relapses being due to viral resistance, although resistance to either ganciclovir (Drew et al., 1991) and foscarnet (Mayers et al., 1993) has been reported.

In a randomized comparative trial, the median time to first progression of disease was similar with ganciclovir and foscarnet (Studies of the Ocular Complications of AIDS Research Group, 1994) but mortality was significantly higher in the ganciclovir recipients (Studies of the Ocular Complications of AIDS Research Group, 1992). The median survival was extended from 8.5 months in the ganciclovir-treated group to 12.6 months in the foscarnet recipients. One possible reason for the difference is the anti-HIV activity of foscarnet (Chrisp & Crissold, 1991). Overall, ganciclovir was better tolerated than foscarnet which requires a longer infusion time and the maintenance of adequate hydration.

There are major problems associated with the iv administration use of ganciclovir or foscarnet. Ganciclovir is myelosuppressive (Buhles et al., 1988) whereas foscarnet is nephrotoxic and may produce electrolyte imbalances (Palestine et al., 1991). These toxicities seem to be less marked in children given ganciclovir (Trang et al., 1993) or foscarnet (Ringden et al., 1986). The choice of parenteral foscarnet or ganciclovir might depend upon the need for concomitant therapies or underlying organ dysfunction: foscarnet being more suitable for those with established neutropenia or needing myelosuppressive drugs and ganciclovir a better choice when renal or metabolic disorders are present. Foscarnet has not yet been studied in paediatric populations with HIV.
A further drawback is the need for an indwelling central Hickman catheter which, together with the need for administration of infusions, may be a burden and have an adverse effect on quality of life. This is a particular problem for young children with HIV and may preclude the use of maintenance anti-CMV therapy. Some of these difficulties may be overcome by the use of portable positive pressure reservoir devices which simplify the delivery of maintenance therapy at home. Direct intravitreal injections of foscarnet or ganciclovir have also been used for patients who have difficulties with standard treatment. Injections of ganciclovir, 200 μg in 0.1 mL of sterile water given twice weekly as induction therapy for 2–3 weeks and then weekly as maintenance therapy, are effective in delaying the progression of CMV retinitis (Cantrill et al., 1989; Ussery et al., 1989; Young et al., 1992; Dhillon, 1994), but multiple injections are associated with an increased risk of endophthalmitis, retinal detachment and vitreous haemorrhage. Intravitreal foscarnet, 1200 μg in 0.05 mL of solution has also been described (Diaz-Lopis et al., 1992). Sustained-release intraocular devices have been developed to prolong the therapeutic effect and to overcome the risks of repeated intravitreal injections. Implants that release ganciclovir at a rate of 2 μg/h for approximately 4 months successfully stabilized CMV retinitis in 90% of 30 eyes (Anand et al., 1993) and, more recently, devices that release ganciclovir at 1 μg/h (and hence last for up to 8 months) have been shown to be effective (Martin et al., 1994). With such devices the risks of septic endophthalmitis are considerably reduced although the risks of retinal detachment are comparable to those with intravitreal ganciclovir. The drawback of any form of local therapy is the lack of protection against CMV disease developing in the other eye or at extraocular sites (Jabs et al., 1989a).

The oral bioavailability of ganciclovir ranges from about 4% to 7.5% for single doses of 500–1000 mg (Markham & Faulds, 1994). It would, however, be more practicable for daily suppressive therapy and this has now been investigated. Preliminary results, comparing the efficacy of oral and iv ganciclovir maintenance therapy have shown that an oral regimen of 500 mg every 4 h was less effective than daily iv ganciclovir (5 mg/kg) in preventing progression of retinitis (86 versus 109 days, respectively, \( P = 0.02 \)) (The Oral Ganciclovir European and Australian Cooperative Study Group, 1995). Another study has shown the two formulations to be broadly equivalent as maintenance therapy (Squires et al., 1995) and the advantages in cost and convenience of oral ganciclovir might outweigh any marginally reduced efficacy. A combination of the ocular implant with prophylaxis against systemic CMV disease provided by oral ganciclovir treatment, might be of further benefit. Other drugs under investigation for the treatment of CMV infections include cidofovir, lobucavir and an anti-CMV monoclonal antibody.

Cidofovir has been shown to have a prolonged and dose-dependent effect on asymptomatic CMV shedding in HIV-positive individuals (a reduction in semen CMV titres of more than 2 log₁₀), but the dose-limiting problem was nephrotoxicity (Lalezari et al., 1994). Further studies of iv cidofovir in CMV retinitis, using concomitant probenecid and prehydration to minimise nephrotoxicity, are underway.

The optimal treatment of CMV manifestations, other than retinitis, in patients with AIDS is not completely resolved. The efficacy of ganciclovir is less clearcut with no prospective studies and only anecdotal reports of responses to treatment of neurological manifestations of CMV disease. Some benefit on colonscopic appearances and CMV shedding was noted in a controlled trial of ganciclovir in CMV colitis but diarrhoea was not improved (Dieterich et al., 1993). It is suggested that for gastrointestinal
disease, induction therapy should be for 2–6 weeks' and that, after a first episode, maintenance therapy is not required (Conant & Wood, 1995).

Primary prevention of CMV disease is not feasible with the currently available compounds although studies of oral ganciclovir and oral valaciclovir are underway.

**Epstein-Barr virus**

Epstein-Barr virus (EBV) is the most prevalent of the human herpesviruses yet discovered, with more than 95% of the world population infected by early adulthood (Henle et al., 1987). Since primary infection usually occurs in childhood, most disease caused by EBV in HIV-positive adults (Table III) is the result of viral reactivation.

Oral hairy leucoplakia (OHL) is a common lesion in HIV-infected individuals, occurring on the lateral border of the tongue in about 30% of adults (Andersson, 1991). EBV DNA and lytic EBV replication can be detected in the middle epithelial cell layers of the tongue. It occurs as a consequence of loss of EBV-specific cytotoxic T cells with increasing immunodeficiency and hence is a useful prognostic marker (Barr et al., 1992). Since the pathogenesis of the condition seems to be related to EBV replication, this may help to explain why antiviral therapy with high dose acyclovir (800 mg qds initially), followed by maintenance therapy with lower doses, is effective (Datta et al., 1980; Greenspan et al., 1986).

Lymphoid interstitial pneumonitis (LIP) occasionally occurs in HIV-infected adults but is primarily a disease of children with HIV-infection (Anderson & Lee, 1988). EBV DNA can be detected in lung biopsies of patients with LIP (Barbera et al., 1992), but it is not clear whether this and the pathological features reflect migration of activated immunocompetent cells from a site of EBV replication elsewhere.

In HIV-infected individuals Hodgkin's disease is more common and there is an extremely high risk of non-Hodgkin's lymphoma compared with HIV-negative persons (Beral et al., 1991; Hessol et al., 1992; Reynolds et al., 1993). Various types of lymphoma are seen (Table III) and in about 50% of all types EBV antigens can be detected (Irwin & Kaplan, 1993). Unfortunately, since there is no evidence of active EBV replication in any of these forms of malignancy, no form of antiviral therapy is of help. Whether prophylactic antiviral drugs with activity against EBV, given early in the course of HIV infection, would reduce the frequency of EBV-associated malignancies is conjectural.

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<th>Table III. Spectrum of EBV disease seen in HIV-positive persons</th>
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<td>Oral hairy leucoplakia (OHL)</td>
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<td>Lymphoid interstitial pneumonitis (LIP)</td>
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<td>Lymphoproliferative malignancies:</td>
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<td>Hodgkin's disease</td>
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<td>Non-Hodgkin's lymphoma</td>
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<td>Burkitt type (small non-cleaved cell)</td>
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<td>Anaplastic large cell (CD30+)</td>
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<td>Angio-immunoblastic lymphadenopathy</td>
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Other herpesviruses

Human herpesviruses 6 and 7 are highly prevalent among HIV-infected persons, and active, widely disseminated HHV-6 infection has been detected at autopsy in AIDS patients (Knox & Carrigan, 1994; Corbellino et al., 1993). Clinical manifestations of disease caused by these viruses in HIV-positive individuals and the potential role for antiviral therapy requires further study.

Recent studies have suggested that a new human gamma herpesvirus, putatively termed human herpesvirus 8 (HHV-8), may be the cause of Kaposi’s sarcoma and other malignancies in HIV-infected individuals (Huang et al., 1995). An infective cause of Kaposi’s sarcoma has long been suspected and there is epidemiological evidence that HIV-infected persons treated with foscarnet for other herpesvirus infection have a lower incidence of Kaposi’s sarcoma than similar groups treated with ganciclovir or acyclovir. A small pilot study of patients with early Kaposi’s sarcoma has suggested that the lesions can regress with foscarnet therapy (Morfeldt & Torssander, 1994).

Co-factors

The immune deficiency resulting from CD4 cell destruction by HIV replication allows the latent herpesviruses to reactivate and cause disease. This disease caused by various herpesviruses acting as opportunistic pathogens is one of the reasons for the use of non-retroviral antiviral therapy in HIV-infected individuals. There is, however, a variety of evidence, some in vitro and some in vivo, suggesting that certain herpesviruses may affect the rate at which HIV replicates and that by inhibiting these herpesviruses, at a time when they are not causing any disease directly, the rate of progression of HIV-induced immune damage may be slowed (Conant & Wood, 1995). An infectious agent interacting at the molecular or cellular level to promote the pathogenicity of HIV in this way can be described as a co-factor.

Among the various ways in which co-factor viruses could interact with HIV (see below) is by allowing HIV replication within the same cells. This can be investigated in a number of ways. Indirect evidence can be obtained from autopsy data from AIDS patients. At the tissue level, cell culture and histopathological examination has shown that CMV (and to a lesser extent HSV) is widely distributed at death (Pillay et al., 1993) and, by the use of the polymerase chain reaction, both CMV and HIV DNA can be detected in more than 50% of tissues (P. Griffiths, personal communication). HHV-6 infection seems to be even more widespread at death in AIDS patients: 85% and 100% of autopsy tissues contained HHV-6 by PCR (Corbellino et al., 1993) or immunohistochemistry (Knox & Carrigan, 1994), respectively. At the cellular level, central nervous system endothelial cells, macrophages and glial cells are frequently co-infected with HIV and CMV (Wiley & Nelson, 1988), and HIV and HSV-1 have been shown to co-infect keratinocytes in skin lesions of AIDS patients (Heng, Heng & Allen, 1994). All these studies show is, of course, that AIDS patients die with herpesvirus infection and not that they die from herpesvirus infections.

There are no in-vivo data to suggest that HIV replication is directly increased in patients with HSV and the mortality in patients with HIV who are coinfected with HSV is not increased. There is, however, some evidence that those infected with CMV progress more rapidly to AIDS. A study from the Royal Free Hospital, London, looked at haemophiliacs infected with HIV (Webster et al., 1989). These patients were chosen
since the date of HIV seroconversion could be determined and the inoculum of HIV could be estimated from the number of units of factor VIII they had received: these factors that could potentially influence disease progression could thus be controlled for. After 9.5 months, 50% of those co-infected with CMV (as determined serologically) had progressed to AIDS, compared with only 18% of CMV-negative patients. Even when this was corrected for age, CMV-positive patients had a 2.5 fold greater risk, of developing AIDS than did CMV-negative patients. There was no such influence of HSV-serostatus on progression to AIDS (Webster et al., 1989).

The theoretical mechanisms by which herpesviruses could interact with HIV have been described elsewhere by Griffiths (1993, 1995). Essentially, they break down into two groups: cell-to-cell interactions and interactions within a single cell. The former interactions are mediated via antigen presentation or cytokine release. For the latter models to apply, the co-factor virus must not rapidly lyse the cell (hence CMV or HHV-6 are more likely candidate herpesviruses than HSV). The commonest of these interactions is via transactivation, although up-regulation of cell surface CD4 receptors or Fc receptors, or the formation of pseudotypes have been described in in-vitro models (Griffiths, 1993).

The most direct evidence for a herpesvirus co-factor comes from double-blind placebo-controlled trials of anti-herpesvirus therapy, measuring the effects on survival when any effect on opportunistic infections is excluded. There have been several such studies of the effect of acyclovir, given in combination with antiretroviral therapy, upon the course of advanced HIV disease. In these studies the progression of disease was assessed by a number of endpoints: surrogate markers such as CD4 count, p24 antigen and β2-microglobulin, the development of opportunistic infections caused by herpesviruses, and death. The initial European-Australian study was a multicentre, double-blind, controlled trial of zidovudine (250 mg four times daily) with acyclovir (800 mg four times daily) or placebo in 131 patients with AIDS and 134 with AIDS-related complex (ARC) (Cooper et al., 1993). The time to development of AIDS, survival and CD4 cell count were assessed. The results showed that there was a statistically significant survival benefit during the 12 month study for those receiving acyclovir in both the AIDS (41% deaths in zidovudine group versus 21% in the combination group, \( P = 0.014 \)) and ARC (12% versus 3%, respectively, \( P = 0.045 \)) patients. This survival advantage was not, however, associated with any significantly better maintenance of CD4 cell counts and there was no decrease in opportunistic infections. Although there were less HSV and herpes zoster episodes in the combination therapy recipients, CMV disease was seen too infrequently in either group for any conclusions to be drawn.

A second European-Australian study was performed to determine whether this survival advantage could be explained by an effect on CMV (Youle et al., 1994). The multicentre, placebo-controlled, double-blind trial of acyclovir (800 mg four times daily) in 302 patients on antiretroviral therapy, who were seropositive for CMV and who had CD4 counts below 150/mm³, assessed both CMV disease and mortality. Essentially, it confirmed the finding of reduced mortality in patients given acyclovir. The study was stopped when sequential analysis showed no improvement in the risk of CMV disease but a significant survival benefit in the group receiving acyclovir: after 1 year of follow-up the mortality in the study group was reduced from 39% to 23% (\( P = 0.018 \)). This reduction was most marked in patients with initial CD4 counts < 50
cells/mm$^3$, but the number of deaths in patients with initial CD4 counts $> 50$ cells/mm$^3$ was too small for any differences between the two groups to be detected.

Combining the results from these two studies and extending the results to the 4 year follow-up showed that the survival benefit of combination therapy was maintained with a hazard ratio of 0.80 (95% CI 0.66, 0.98) (Cooper et al., 1994).

A retrospective analysis has been undertaken of the effect of acyclovir on survival and disease progression among HIV-positive individuals in the US Multicenter AIDS Cohort Study (MACS), which has been monitoring homosexual men since 1984 (Stein et al., 1994). The gathering of data was by 6-monthly questionnaires between 1987 and 1992, and once a person indicated on the questionnaire that they were taking acyclovir it was assumed that they were always on the therapy. Acyclovir therapy was not associated with any retardation of CMV disease or development of AIDS but significantly prolonged survival ($P < 0.01$) when the patient had described its being used 'to fight HIV or AIDS' (a reason offered on the questionnaire and described as the 'AIDS indication' in subsequent analyses). There was a trend towards better survival in persons taking acyclovir for any indication ($P = 0.07$). If the acyclovir was started after AIDS had been diagnosed then acyclovir had a significant survival benefit, whether used for any indication ($P = 0.007$) or for the 'AIDS indication' ($P = 0.005$). Longer uninterrupted use of acyclovir was associated with longer survival but there was no dose effect, $< 600$ mg/day seemingly as effective as larger or unknown doses.

The questions about the optimum dose and the uncertainty about the mechanism behind the survival benefit from acyclovir have led to a continuing debate about how best to use this information. It was hoped that some answers would be obtained from a trial commenced under the auspices of the AIDS Clinical Trials Group (ACTG204). The trial had the primary endpoints of CMV disease and survival and there were three arms. Patients in one arm of the study were given high dose acyclovir (800 mg qds) as in the previous studies. Those in the second arm were given low dose oral acyclovir and those in the third arm the L-valine ester of acyclovir, valaciclovir, at a dose of 2 g qds (which produces very high blood levels of acyclovir). It was hoped that the very high concentrations of acyclovir from valaciclovir would provide better control of CMV. Furthermore, the different doses of acyclovir used in the trial would attain very different serum concentrations and might control replication of different herpesviruses. By this means it might be possible to define the burden of each herpesvirus in AIDS patients and determine if reduction in a particular viral load explained the improved survival. Unfortunately, the trial was halted after an interim analysis of the data showed an increased mortality in the valaciclovir arm after a median analysis of 9 months. Full interpretation of the results is difficult since, although treatment with valaciclovir was associated with reduced survival, there was a delay in time to CMV disease and HIV progression was the only cause of death that was more common in the valaciclovir recipients. Valaciclovir recipients also stopped their therapy earlier, suggesting that the valaciclovir dose used (eight times greater than that proposed for genital herpes) exceeded that tolerated by severely ill patients. Further analysis of the data is underway and other studies of valaciclovir in HIV-infected populations continue.

At present, therefore, all human herpesviruses remain candidates for the co-factor effect that explains the excess mortality in AIDS patients.
References


