in 1991 were 200,000. For enteric organisms short antibiotic courses apply less selection pressure than longer courses. Similarly in Western settings vancomycin resistance is spreading and some *Staph aureus* is now virtually untreatable.

Recognised pathogens were found in 46 per cent of US students who had diarrhoea while visiting Mexico, ETEC comprised 63 per cent of the total, with shigella in second place at 21 per cent and salmonella third at 6 per cent. An extensive survey of potable water samples in Greece showed no evidence of *0157 E. coli* suggesting that this form of *E. coli* is not transmitted through water contamination. The preferred treatment for travellers diarrhoea is loperamide plus quinolone. Zalderide, a calmodulin inhibitor with gastro-intestinal anti-secretory properties was as effective as loperamide. Cyclospora is now a recognised cause of prolonged diarrhoea in Nepal and other countries. In a trial of cotrimoxazole after seven days only 6 per cent were shedding cylcospora in the treated group compared to 88 per cent in the placebo group.

Miscellaneous

An assault is a major health risk for long term expatriates and risk factors have been examined in US Peace Corps Volunteers (PCV). Thirty one per cent were aggravated (weapon used or hospitalisation required), 31 per cent were simple assault, 17 per cent were completed or attempted rape and 21 per cent were other sexual assaults. Single PCVs were 4 times more likely to be assaulted than were married, men 6 times more likely to be injured than women and injury was more likely in those who had misused alcohol. Most sexual assaults involved single white women and resistance (particularly vigorous verbal protest) decreased the likelihood of completed rape by about seven times. A minority but high proportion of rapes were preventable and due to risk increasing behaviour, for instance walking home alone late at night.

The potential for pulmonary emboli arising from cramped seats on long over night flights was emphasised by five cases of the economy class syndrome. Ages ranged from 25 to 75 but four were under 40 and one died. As a World Traveller Class BA passenger I took 300 mg soluble aspirin on both main flights. A poster documented the stability of paracetamol at high ambient temperatures and a 35 per cent degradation of aspirin after 30 days at 50°C.

Liverpool tropical physicians reported two unusual cases of Lake Malawi acquired *S haematobium* manifesting with Katayama fever. Rectal biopsies to exclude the possibility of combined *S haematobium* and *S mansoni* infestation were apparently not performed. Researchers at the London Hospital for Tropical Diseases reported contrasting sensitivity of serum schistosomal ELISA, for *S mansoni* 94 per cent and *S haematobium* 63 per cent. The relationship of false negatives to the probable timing of infection was not clarified. *S haematobium* sometimes has an extended seronegative window and some of the apparent seronegatives might have seroconverted later if further specimens had been performed. One third of PCVs swimming in Lake Malawi are infected.

The Medical Advisory Service for Travellers Abroad group (MASTA) reported on toxicology and efficacy studies for their non-DEET eucalyptus extracted Mosiguard Natural insect repellant. It appears to be comparable to DEET both for insect repellant activity, duration of action and to be safe.

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ANTIRETROVIRAL THERAPY: A REVIEW

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Human immunodeficiency virus (HIV) infection represents a global pandemic. The World Health Organisation has estimated that over 18·5 million adults and 1·5 million children are now infected with over 4·5 million cases of acquired immunodeficiency syndrome (AIDS).[1] Significant progress has been made in understanding the biology of HIV and the pathogenesis of the resulting disease. Clinical evidence suggests that treatment with antiretrovirals can delay progression of the disease and prolong survival[2,3] but development of new treatments have been hampered by drug resistance, treatment intolerance and the limited validity of available surrogate markers for assessing disease progression.

HIV is a retrovirus consisting of a protein core surrounded by a lipid envelope. There are two types of HIV, 1 and 2, and although both types are known to cause AIDS, infection with HIV-1 is more common in Western Europe, Australasia and the United States of America. HIV possesses a diploid single stranded RNA genome comprising genes common to all retroviruses; *gag, pol* and *env*. In addition, HIV-1 contains unique extra genes, including *tat, rev* and *nef* which act as regulators of replication. Embedded in the lipid envelope of the virus is the glycoprotein gp 120 which binds preferentially to CD4 molecules. CD4 molecules are present most commonly on T4 lymphocytes but also occur on macrophages, monocytes and dendritic cells which may also be infected with HIV.

After binding with CD4 receptors the virus fuses with the cellular membrane releasing its core proteins and viral RNA into the cytoplasm. A virion associated enzyme, reverse transcriptase (RT), catalyses the synthesis of a double stranded DNA copy using the viral RNA genome as a template. The DNA is subsequently incorporated into the host genome by viral integrase. Here it results in the synthesis of new viral particles by repeated transcription into RNA. HIV protease is responsible for post-translational processing of polyproteins into the structural proteins and enzymes of the mature virus. Hence, by understanding the life-cycle of HIV, potential targets for anti-HIV therapeutic agents have been identified.

HIV attachment

Agents that bind to either viral gp120 or host CD4 molecules are able to disrupt binding of the virus to the host cell. Agents such as recombinant soluble CD4 (rsCD4) and other CD4 analogues have been devised to bond to viral and cellular gp120, and many of these agents have significant antiretroviral activity *in vitro*,[4–6] although their effects *in vivo* are less clear.[7]

HIV penetration and uncoating

The aromatic polycyclic diones, hypericin and pseudohypericin to prevent penetration and uncoating of HIV-1 in the presence of visible light illumination.[8] The clinical relevance of this interaction remains unclear.

Proviral DNA synthesis catalysed by reverse transcriptase

The synthesis of double stranded proviral DNA from viral RNA is catalysed by reverse transcriptase (RT) and the inhibition of this enzyme is the cornerstone of current antiretroviral therapy. There are two broad categories of RT inhibitors. Nucleoside analogue RT inhibitors are Zidovudine (also known as azidothymidine, AZT), 2,3dideoxyinosine (ddI), 2,3dideoxycytidine (ddC), stavudine (d4T) and lamivudine (3TC). Of these AZT, ddI and ddC are the only antiretroviral agents currently licenced in the United Kingdom for the treatment of HIV infection. Nucleoside analogues undergo intracellular phosphorylation to triphosphates which compete with host-cell triphosphates for binding to the RT enzyme. Incorporation of these nucleoside analogue triphosphates into the DNA chain then leads to chain termination preventing proviral DNA synthesis.

Non-nucleoside RT inhibitors (NNRTIs) are Delavirdine (DLV), Loviride, Tibo and Nevirapine. NNRTIs inhibit the activity of RT by noncompetitive binding close to the active-site catalytic residues. They are not incorporated into the DNA chain. Early clinical experience with NNRTIs has demonstrated potent antiviral activity and a high therapeutic index, but resistance by the virus develops quickly. Nevertheless, several promising new agents in this category are being developed. Overall these drugs are thought to be better tolerated than most of the licenced nucleoside analogues.

Integration of proviral DNA into the host genome

A number of experimental agents have been shown *in vitro* to inhibit viral integrase, preventing integration of double stranded proviral DNA into the host genome.[9] Further research into this potentially important target appears warranted.

Viral transcription and translation

Protease inhibitors, Saquinavir, Ritonavir (AB7-538) and Indinavir (MK-639), are the most promising agents currently under clinical evaluation. They prevent the assembly of mature infectious virions hence interrupting viral spread.[10] They have been shown to be highly effective *in vitro*[11] and are generally well tolerated by patients with few side effects.[12] Most of the current protease inhibitors in clinical trials are being administered concurrently with other antiretroviral agents.

Other therapies including gene therapy are being targeted at viral *tat* and *rev* proteins which regulate HIV replication.[13,14] Research is also underway in the development of antisense oligonucleotides that specifically bind to complementary viral RNA or proviral DNA and interfere with its expression.[14]

Viral assembly and release

Recombinant interferon alpha (IFN-α) has been shown to be beneficial in early HIV infection,[15] where significant reductions in p24 antigen concentrations have been demonstrated. It is thought to act primarily by interfering with viral assembly and release,[16] but may also have effects earlier in the life-cycle of HIV.[17] Due to its adverse effects (influenza-like symptoms, granulocytopenia, deranged liver function) its use has been limited. It may have a role to play when given in combination with other antiretrovirals.

In the UK only three antiretroviral agents have been licenced for use; AZT, ddI and ddC. In addition, Saquinavir, 3TC and d4T may be obtained on a named patient basis. A particular problem which has recently been examined is viral resistance to the various antiretroviral agents. Various factors such as rapid viral replication, inherent inaccuracies introduced by the RT enzyme the pre-existance of mutant forms and selective pressure induced by antiretroviral therapy have all been cited as possible causes of resistant virus.[18,19]

Traditionally, antiretroviral therapy has been administered as monotherapy. However recent evidence suggests that patients are likely to benefit from combination therapy. The Delta study[20] concluded that in individuals with HIV infection with AIDS related complex (ARC) or AIDS with a CD4 count of $>50\,mm^3$ who had no previous experience of antiretroviral agents, treatment with combinations of AZT and ddI or AZT and ddC were more likely to limit progression of disease and increase survival compared to individuals on monotherapy with AZT. No similar benefit was observed in individuals who had previously been on AZT for more than three months.

In the AIDS Clinical Trials Group (ACTG) study,[21] 175 individuals with HIV infection and CD4 counts of $200–500\,mm^3$ were given either monotherapy with AZT or ddI, or combination therapy with AZT/ddI and AZT/ddC. In both AZT naive and experienced subjects, AZT/ddI, AZT/ddC and ddI were each superior to monotherapy with AZT. There was also a trend in this study in favour of immediate combination therapy in AZT naive patients. It is also of note that the incidence of adverse events in those receiving combination therapy was not significantly higher than those on monotherapy.

The role of combination therapy involving some of the newer agents will need to be addressed urgently. Already there is evidence to suggest that combination therapy with AZT and 3TC may be the most potent antiretroviral combination to date.[22] Other research is currently examining the merits of a combination of three or four agents. While researchers strive to develop newer agents and study the merits of various drug combinations, it remains unclear when therapy should be initiated. While some advocate combination therapy when an individual is diagnosed HIV positive, including treatment of the primary infection, others delay therapy until an individual becomes symptomatic or develop other signs of disease progression e.g. falling CD4 count or rising HIV RNA titre (a falling CD4 count would signify greater immune supression and a rising HIV RNA titre increased viral load).

Managing antiretroviral therapy in patients with HIV disease is an ongoing challenge. Ultimately, it is hoped that drug regimens and strategies will suppress HIV enough to improve patients' long term survival, asymptomatic from the disease with minimal side-effects. In order to achieve this, the regimen should address the problems associated with the development of drug resistance and toxicity. At present, specific strategies for treatment must be individualised on the basis of disease stage, clinical status and perhaps most importantly quality of life.

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I BELIEVE...

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My initial response to the editor's request for a contribution to this series on *I Believe* was 'not much'. However, after a little of what passes in my mind for thoughtful reflection, I came to think that my paucity of beliefs was not entirely an intrinsic state but more the outcome of the 'action-orientated' life that clinicians, and particularly surgeons, tend to live. A professional career spent in *doing* rather than *contemplating* does not leave much time for reflection although this could be regarded as a poor excuse—more thought might lead to better deployment of plans of action. In addition, short-term thinking to anticipate and to solve (one hopes) day to day problems, crowds out longer term contemplation of our nature and *being*. In the British of my generation this has been combined with reticence and also a faint embarrassment about being committed to something without having evidence to support it. For that is what, in my view, constitutes a 'belief'. It could equally well be called a starting point, assumption or value, 'givens' or standards which preside over the way we conduct our lives. I leave to others any debate on whether these things are built in to our biological nature (*hard wired* in modern jargon) or acquired by cultural exposure, although I favour nurture rather than nature. The latter carries with it Jungian-like creation of a collective cultural attitude which is inherited through social, rather than strict, biological means. However, I think that what is now fashionable to call neo-Darwinism would seek to blend cultural change with biological on the grounds that advantageous social adaptations to the environment favour certain individuals and so lead to their selective success.

Beliefs are largely positive; lack of them is negative and dismissive but nevertheless often easier to state. The latter are often founded on scepticism to which I will return. Among my 'not-beliefs' is the lack of a conventional religious one. Our observations of the Universe 'out there' (believing as I do that there are grounds—although as Bishop Berkeley was inclined to think uncertain ones—for thinking that there is such a Universe), makes me consider that things are too complicated to be explained by adherence to the concept of a God or gods such as those specifically created by individual religions. Religions may be a necessary part of our social existence and can occasionally set moral guidelines which are of importance in our reactions to others. However, although there may be religious purpose in a world of chance[1] and this may ultimately yield a better understanding of our position in the nature of things, I believe that we

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