MIXED BAG

## MULTIDRUG RESISTANCE AND RAPID PROGRESSION TO AIDS: A PUBLIC HEALTH NIGHTMARE

An HIV case from New York has hit the headlines recently, with the lay press talking of a 'new and more virulent' strain of HIV. A recent edition of the *Lancet* carries this case report, placing this individual's infection into perspective, albeit a rather worrying one from the point of view of public health. Martin Markowitz and colleagues report on 1 patient, assessed between December 2004 and February 2005, with documented HIV-1 seroconversion, who rapidly progressed to AIDS. The susceptibility of his HIV-1 to antiretroviral drugs was assessed using genetic sequencing and phenotyping.

To understand this process better it is worth knowing that HIV-1 is classified as either non-syncytium inducing or syncytium inducing, and identification of chemokine receptors CCR5 and CXCR4 as a necessary entry co-factor has provided a mechanistic explanation for the difference between these virus types. CCR5-tropic viruses that are non-syncytium inducing dominate in early HIV-1 infection, while strains that use CXCR4 as a co-receptor are generally syncytium inducing and are found in about one-half of the patients who progress to AIDS. This latter strain is uncommon in newly infected people. The natural history of HIV-1 infection is widely variable and is affected by viral and host factors. It is usually years before AIDS develops, but there are reports of rapid progression to AIDS and in some of these patients CXCR4-tropic or dual-tropic viruses were identified at seroconversion. This suggests that these strains are associated with a faster clinical course. This patient is a case of infection with a multidrug-resistant, dual-tropic HIV-1 virus that resulted in progression to AIDS in 4 - 20 months.

The patient is a 40-year-old man who has sex with men. He was negative in multiple tests for HIV-1 antibodies between September 2000 and May 2003 and his absolute lymphocyte counts during this time were normal. However, in early November 2004 he developed fever, pharyngitis, weakness and fatigue for about a week. A few weeks later, intractable sore throat, fatigue and malaise recurred and he was diagnosed HIV-1 positive. A follow-up visit in late December 2004 showed a CD4 T-cell count of 80 cells/µl, a CD8 T-cell count was 1 012 cells/µl and the concentration of HIV-1 RNA in his plasma was 280 000 copies/ml. When seen again in January 2005 he reported sore throat, difficulty swallowing, severe fatigue, weight loss and a general feeling of being unwell. Physical examination was normal, but repeat HIV-1 testing confirmed the infection. Results of a detuned enzyme immunoassay were positive, indicating that this infection was beyond the acute or primary phase. Several viral loads and CD4 counts were determined which suggested that the man had already progressed to symptomatic AIDS with profound CD4 T-cell depletion. Because of this rapid course the investigators took a more detailed history. It emerged that he had been sexually active with many male partners over the years, often in conjunction with metamphetamine use. He traced his infection to a week in October 2004 when he had sex with multiple partners. Sexual activity continued until the end of December 2004 when he felt too unwell to continue.

The authors point out that while rapid progression to AIDS and transmission of multidrug-resistant viruses have both been previously described, this case shows both features in one individual. The duration of this man's infection cannot have been longer than 20 months. The transient febrile illness in early November 2004, starting about 2 weeks after a series of high-risk sexual contacts with multiple partners, could have been the first sign of primary HIV-1 infection. In this case, the duration of infection would be 4 - 5 months. These facts, coupled with the detuned antibody assay suggesting recent infection, led the authors to believe that their patient had been infected for between 4 and 20 months. They asked if his rate of deterioration is noteworthy and found that a review of the data suggests that it is. They also asked if the rapid progression could be explained by the properties of his unique HIV-1 varients. The patient has a mixture of CCR5-tropic and dual-tropic HIV-1 populations. The virus grows well *in vitro* and has a greater replication capacity than many wild-type viruses. These *in vitro* characteristics, along with the great depletion of CXCR4+ T-cell population *in vivo*, suggest that this strain of HIV-1 may be particularly aggressive. However, their genetic studies are still in process and they acknowledge that knowledge of host determinants of rapid progression is incomplete, so conclude that the reasons for the clinical course seen in this man are still unclear.

Treatment options for this patient are limited because his virus is resistant to all protease inhibitors and nevirapine and is sensitive to enfuvirtide and efavirenz. Phenotypically, the virus is susceptible to various NRTI-class drugs. However, *in vitro* studies suggest that most NRTIs will be ineffective *in vivo*. The patient has been started on a multidrug regimen that includes enfuvirtide and efavirenz.

The potential public health ramifications of this case are large. Because of his history of multiple sexual contacts and metamphetamine use, the New York City Department of Health and Mental Hygiene issued an alert to local doctors on 11 February 2005. The patient's sexual contacts are being traced. Until further investigations have been done it will not be possible to say whether or not this is an isolated case.

Markowitz M, *et al. Lancet* 2005; **365Z:** 1031-1038.

## Low-dose aspirin and cardiovascular disease in women

At last, a randomised trial of the primary prevention of cardiovascular disease in women using low-dose aspirin. Some time ago, my aunt, living in Australia, contacted me to ask whether or not she should be taking aspirin. To be honest, I really couldn't tell her what the evidence showed and suggested that she discuss the pros and cons with her doctor. Her doctor suggested that she take it. Now we have some evidence to consider rather than just pulling suggestions out of thin air.

Paul Ridker and colleagues point out that randomised trials have shown that low-dose aspirin decreases the risk of a first myocardial infarction in men, with little effect on the risk of ischaemic heart disease, but say that there are few data on women. The team randomly assigned 39 876 healthy women, aged 44 or older, to receive 100 mg of aspirin on alternate days, or placebo. They then monitored them for 10 years for a first major cardiovascular event (a non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular disease).

During follow-up, 477 major cardiovascular events were confirmed in the aspirin group compared with 522 in the placebo group. This is a non-significant reduction of 9% in those taking aspirin. However, there was a 17% reduction in the risk of stroke in the aspirin group compared with the placebo group, caused by a 24% reduction in the risk of ischaemic stroke, coupled with a non-significant increase in the risk of haemorrhagic stroke. But, compared with placebo, aspirin had no significant effect on the risk of fatal or non-fatal myocardial infarction or death from cardiovascular causes. The adverse event of gastrointestinal bleeding requiring transfusion was more frequent in the aspirin group than in the placebo group. However, analysis of women 65 years or older showed that aspirin significantly reduced the risk of major cardiovascular events, ischaemic stroke and myocardial infarction.

So, it would appear that in women over 65 there is a positive outcome associated with low-dose aspirin in terms of cardiovascular disease, but in younger women, the main effect is on ischaemic stroke. Quite a useful guideline.

Ridker P, *et al*. *NEJM* 2005; **352:** 1293-1304.

## Exercise, stress management and cardiovascular disease risk markers

Another area where there are plenty of assumptions and often limited evidence is the effect of behavioural interventions on the risk of cardiovascular disease. James Blumenthal and colleagues investigated the effect of 2 behavioural programmes, aerobic exercise training and stress management training, compared with routine medical care on psychosocial functioning and markers of cardiovascular risk. They point out that there are observational studies that show that psychosocial factors are associated with increased risk of cardiovascular morbidity and mortality, but that the effects of behavioural interventions on psychosocial and medical end points are uncertain.

They carried out a randomised controlled trial of 134 patients (92 men and 42 women aged between 40 and 84 years) with stable ischaemic heart disease (IHD) and exercise-induced myocardial ischaemia between January 1999 and February 2003. The interventions were routine medical care (usual care), usual care plus supervised aerobic exercise training for 35 minutes 3 times a week, and usual care plus weekly 1.5 hour stress management training for 16 weeks. They rated participants' self-reported measures of general distress and depression, and measured left ventricular ejection fraction (LVEF) and wall motion abnormalities (WMAs), flow-mediated dilatation, and cardiac autonomic control.

The results showed that patients in the exercise and stress management groups felt better generally and had less depression that those given the usual medical care. They also showed smaller reductions in LVEF during mental stress testing. Exercise and stress management were associated with a lower incidence of WMAs and improvements in flow-mediated dilatation.

The conclusion was that for patients with stable IHD, exercise and stress management training reduced emotional distress and improved markers for cardiovascular risk more than routine medical care.

Blumenthal JA, *et al*. *JAMA* 2005; **293:** 1626-1634.

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