AIDS briefs

TB does not always increase viral load*

A recent study published in the *Journal of Acquired Immune Deficiency Syndromes* shows that one-quarter of Ugandan patients co-infected with TB and HIV had a viral load below 10 000 copies/ml. TB is usually associated with an increase in viral load.

Two studies involving a total of 202 HIV-positive patients with sputum smear-positive TB were reported by the investigators. Median baseline viral load was approximately 40 000 copies/ml and the median CD4 cell count was 472 cells/mm^3.

However, 49 patients had a baseline viral load below 10 000 copies/ml, with 12 of these individuals having a viral load below 1 000 copies/ml.

The investigators compared the 40 patients who had a viral load below 10 000 copies/ml to the 153 individuals with higher viral loads. There was no difference between these patients with regard to age, sex or severity of TB disease. Nor did CD4 cell count differ.

The investigators then looked at the effect initiating TB therapy had on viral load. When TB treatment was started, 19 (21%) of these patients had a viral load below 10 000 copies/ml. The investigators found that after 3 months of TB therapy, patients whose baseline viral load was above 10 000 copies/ml were significantly more likely to experience a fall in their viral load of at least 0.5 $\log_{10}$ (p=0.001).

However, patients whose viral load was below 1 000 copies/ml when they started TB treatment were significantly more likely than patients with a higher baseline viral load to experience an increase in their viral load of at least 0.5 $\log_{10}$.

The investigators note that multiple studies have observed an association between active TB and higher viral load. They write, 'Contrary to these observations, we detected low-level HIV viremia… in almost 25% of Ugandan patients with untreated HIV-TB coinfection in 2 different clinical trials and found that low-level viremia was not related to baseline CD4 cell count or severity of TB.'

They conclude that investigation of 'host and viral factors may shed further light on potential causes of low-level HIV viremia in the setting of active TB and provide additional insights into HIV and TB pathogenesis'.

Srikantiah P, *et al. J Acquir Immune Defic Syndr* 2008; 49: 458-460.

HIV prevalence may decline because the most vulnerable will die first*

A recent study, published in *AIDS*, suggests that the declines in HIV prevalence seen in some countries may be due to differences in people's susceptibility to the virus rather than behaviour change. The study reports on a mathematical model based on a survey of Kenyan sex workers.

The model suggests that HIV infections early in an epidemic occur more frequently in people who are genetically susceptible to the virus. With time, most of these people will be infected and so the virus is passed on to those who are less genetically vulnerable. This results in large declines in incidence, and, as the genetically susceptible first-generation people die, a decline in prevalence.

HIV prevalence has declined in several African countries in the last decade, e.g. from 31% to 16% in Zimbabwe and 14% to 5% in Kenya. In India, prevalence is estimated to have halved. A similar phenomenon in Uganda in the 1990s was attributed to behaviour change.

What alerted researchers to the idea that this may not be due to behaviour change was a long-term longitudinal study of Nairobi sex workers who were initially HIV negative. HIV incidence declined without any change in sexual risk behaviour. In this study the risk of acquiring HIV per sex act declined fourfold between 1985 and 2005, from one infection per 225 sex acts in 1985 to one per 1 000 in 2005. This cannot be explained by a difference in HIV prevalence among the sex workers' clients, as it pre-dated HIV prevalence declines in the Kenyan male population by a decade.

The authors hypothesised that HIV incidence might be declining because the virus was disproportionately infecting the most genetically vulnerable women first. They devised a model of a typical African population. They divided the population into high-risk persons (namely female sex workers and their clients) and the general population, and modelled movement between these groups. They then modelled the way the epidemic would develop if they divided this population into three groups of 30% each, who could be respectively infected with HIV easily, quite easily, and with difficulty, and 10% (a deliberate overestimate in order to build the most conservative estimates of susceptibility to infection into the model) who were completely resistant to infection.

They found that a version of this model almost completely explained the observed decline in infections seen in the Nairobi female sex workers and fitted fairly closely the observed increase and later decline in prevalence in the general Kenyan population.

The model implies that predictions about the spread of a mature epidemic may result in serious overestimates if they are based on the infection rate seen in the first few years of the epidemic and may explain the lower-than-expected infection rates in some prevention trials. And, of course, that the effectiveness of some prevention programmes may have been overestimated.

Nagelkerke NJD, *et al. AIDS* 2009; 23: 125-130.

Kimani J, *et al. AIDS* 2008; 22: 131-137.

Excellent adherence in Africa due to social networks

Keith Alcorn

The very high levels of adherence to antiretroviral therapy observed in some settings in sub-Saharan Africa appear to be explained by the need to preserve a network of social relationships that people

with HIV rely upon to survive, rather than being a consequence of individual motivation, according to a study conducted in Nigeria, Tanzania and Uganda.

The findings, published in the open access journal *PLoS* Medicine, come from an ethnographical study in which 252 patients, treatment partners and health care professionals were interviewed at three treatment sites (Jos, Nigeria; Dar es Salaam, Tanzania; Mbarara, Uganda).

The researchers, led by Norma Ware of Harvard University, conducted interviews designed to understand the patients' views of adherence, of clinic visits and of help received from treatment partners. Health care providers were asked about clinic visits and how the topic of adherence emerged during these visits, and about their perceptions of barriers to adherence. Treatment partners were asked about the types of help they provided, what impact they thought it had, and their feelings about being a treatment partner. The questions were unscripted in order to allow unanticipated themes to emerge.

Interviews were reviewed to identify key obstacles to adherence and the ways in which these obstacles were negotiated by individuals.

The biggest obstacles to adherence were those caused by a scarcity of resources – money for transport to the clinic and food for self and family – and these obstacles had to be overcome by borrowing money or going without food in order to maintain good health through excellent adherence.

But maintaining good health was not an end in itself, the interviews revealed. Ill-health placed a burden on others, and placed the individual at risk of losing support from others – support that in times of good health was critical for overcoming hardships distinct from HIV. Good adherence and good health reduced the calls on the goodwill of others, and made it more likely that when future needs arose potential helpers would be willing to help.

Poor adherence on the other hand was perceived as letting down helpers, and by raising the spectre of ill-health, caused individuals to question whether family and neighbours might abandon them or downgrade their needs if they became burdensome.

Health care providers revealed that they too offered help above and beyond their roles, by providing money for transport, by keeping clinics open late to accommodate latecomers, or by providing food at their own expense. But in return, providers expected good adherence, and made this known to patients. Some health care providers said that they had threatened patients with discontinuation of treatment if they persistently failed to take medication.

Treatment partners had a similar expectation of good adherence in return for their help.

The authors say their findings suggest the importance of social capital – trust, co-operation, reciprocity and sociability – in maintaining adherence. Social capital also explains the fear of stigma, they argue, because stigma isolates people from social relationships that would improve the chances of survival. Hence the strenuous efforts to avoid stigma, even at potential long-term costs to the individual.

'Adherence preserves social capital by protecting relationships required for survival in settings of poverty. This may be what patients are referring to when they tell us they have "no choice" but to adhere,' the authors conclude. They note that their findings may not be applicable to all settings in Africa, and urge further research on social capital in order to guide interventions that will maintain adherence and sustain treatment effectiveness.

Ware NC, *et al*. Explaining adherence success in sub-Saharan Africa: an ethnographic study. *PLoS Medicine* 2009; 6 (1): e10000011. doi:10.1371/journal.pmed.1000011 (this article is adapted from NAM/www.aidsmap.com).

Cancer is an increasingly important cause of death among people with HIV

Michael Carter

Over one-third of deaths in HIV-positive patients in France in 2005 were caused by cancers, investigators report in a study published in *Clinical Infectious Diseases*. This represents a significant increase in the proportion of cancer-related deaths among French HIV-positive patients since 2000.

The investigators suggest that better cancer prevention, monitoring and care could help reduce the number of deaths caused by malignancies in patients with HIV, and also stress the importance of keeping the CD4 cell count of HIV-positive individuals above 250 cells/mm^3.

Thanks to HIV treatment, there has been a significant fall in the amount of HIV-related illness and death seen in HIV-positive individuals in industrialised countries. Rates of the AIDS-defining cancers, non-Hodgkin's lymphoma and Kaposi's sarcoma, have also fallen.

However, as patients with HIV live longer, it is expected that conditions such as heart disease, liver problems and non-HIV-related cancers will become increasingly important causes of death.

In 2000, a survey of French hospitals (the Mortalité study) revealed that 12% of all deaths in HIV-positive individuals were attributable to non-HIV-related cancer and that cancers accounted for 29% of all deaths in patients with HIV.

Investigators repeated this survey in 2005.

A total of 1 042 deaths were reported in 2005 among the 78 000 individuals receiving HIV care at hospitals participating in the study – compared with 964 deaths in 2000.

Details of 1 013 were available for analysis by the investigators. Overall, 76% of deaths were in men, the median age was 46 years, and the median duration of diagnosed HIV infection was 12 years. Most of the patients (87%) had received HIV treatment and 47% had a viral load below 500 copies/ml at the time of death. Median CD4 cell count was 161 cells/mm^3, indicating moderately severe immune suppression. This was, however, higher than the median CD4 cell count of only 90 cells/mm^3 recorded in patients dying in 2000.

The most frequent cause of death was an AIDS-defining illness (total number 377 (36%), a fall from 47% in 2000). In all 344 (34%), deaths were cancer-related. This represented a significant (p=0.02) increase from 2000 when 29% of deaths were cancer-related.

Further analysis showed that 17% of deaths were caused by cancers that were not related to either HIV or hepatitis. Patients dying of such cancers had a median age of 49 years, had been diagnosed with HIV for a median of 12 years, had a median CD4 cell count of 200 cells, and 55% had a viral load below 500 copies/ml at the time of death.

A total of 64 deaths were caused by respiratory cancers, including 53 caused by lung cancer and 12 by cancer of the nose or throat. There was no change in the proportion of deaths caused by respiratory cancers in 2005 (5%) compared with 2000 (6%). Lifestyle factors appear to have been important in these deaths as 90% of those dying of respiratory cancers were smokers and 34% drank excessive amounts of alcohol.

There was a significant increase in the proportion of deaths caused by digestive cancers in 2005 compared with 2000, including 10 cases of pancreatic cancer compared with just 3 in 2000.

The investigators noted that there were 7 cases of breast cancer in 2005 compared with none in 2000, and there was also an increase in the number of deaths attributable to skin cancer (10 in 2005 compared with 2 in 2000). There was no change in the number of deaths attributable to anal cancer.

Death from liver cancer was mainly associated with hepatitis C virus infection. This contrasted with 2000 when hepatitis B virus was also an important cause of liver cancer-related death.

There was no difference in the proportion of deaths caused by non-Hodgkin's lymphoma between 2005 (11%) and 2000 (10%). The CD4 cell counts of individuals dying of these cancers in 2005 and 2000 were also comparable (86 cells/mm^3 v. 76 cells/mm^3). However, almost one-third of patients dying of this type of cancer had a CD4 cell count above 200 cells/mm^3 at the time of death.

Kaposi's sarcoma accounted for 4% of cancer deaths in 2005 compared with 3% in 2000, a non-significant change. Fewer than 1% of cancer deaths in both 2005 and 2000 were caused by cervical cancer.

'We demonstrated that malignancies accounted for more than one-third of the causes of death in this population of patients. We also demonstrated that the proportion of deaths attributable to malignancies increased significantly since 2000,' write the investigators.

They emphasise that 'the proportion of non-AIDS-related cancers also increased significantly from 2000 to 2005'. Other studies, such as the D:A:D study, have found that non-AIDS-defining cancers are an increasingly important cause of death in patients with HIV. The investigators note similarities between the findings of their study and those of the D:A:D study, particularly that the median CD4 cell count of patients dying of non-AIDS-defining cancers was in the region of 200 cells/mm^3.

The investigators conclude that 'cancer prevention, screening, early diagnosis and improved management and surveillance should be included in routine long-term follow-up of HIV-infected patients and should have some immediate impact on mortality'. They also stress the importance of keeping the CD4 cell count of HIV-positive individuals above 250 cells/mm^3.

Bonnet F, *et al.* Changes in cancer mortality among HIV-infected patients: the Mortalité 2005 survey. *Clin Infect Dis* 2009; 48 (online edition) (this article is adapted from NAM/www.aidsmap.com).

BRIDGET FARHAM

Single Suture

Overworked protein may be common key to ageing

An overworked protein that causes yeast to age when it neglects one of its functions may also trigger ageing in mice. If the same process operates in people, it may suggest new ways to reverse age-related disease.

Ageing causes genes to be expressed in the wrong tissues across the body. This is the process that is thought to contribute to diseases such as diabetes and Alzheimer's. We know that sunlight or chemicals may cause limited DNA damage, but it is not clear how these more widespread changes in gene expression occurred.

David Sinclair and colleagues at Harvard Medical School in Boston started looking at yeast cells to elucidate this mechanism. Yeast produces a dual-function protein, Sir2, that is involved in DNA repair and also helps to keep certain genes switched off. As yeast cells age, the protein can't do both jobs and neglects its role as a gene suppressor.

Sinclair's team have now shown that SIRT1, the mammalian version of Sir2, also begins to neglect its gene-suppressor role in mice whose DNA is damaged and that this may contribute to ageing. This looks like a common mechanism of ageing.

It is possible that gene-suppressing proteins may become overworked in people as they age, and could be targets of drugs to keep us young. Mice that were engineered to overexpress the gene for SIRT1 were better at repairing DNA, more resistant to cancer and maintained a more youthful pattern of gene expression.

New Scientist, 29 November 2008: 18.