AIDS briefs

Lower CD4 counts at diagnosis may point to increased HIV virulence

MICHAEL CARTER

The initial CD4 cell counts of patients newly infected with HIV fell significantly between 1985 and 2001, US research published in the 1 May edition of *Clinical Infectious Diseases* has shown. This suggests that the virus may have evolved to become more virulent during this time period, which could have clinical implications, shortening the interval between infection with HIV and the need to start HIV treatment.

In people with HIV, CD4 cell counts provide an important indication of the strength of the immune system, of HIV disease progression and of when to start antiretroviral treatment.

At the time of HIV infection a massive loss of CD4 cells occurs. The immune system then mounts a response to HIV, virus levels fall, and the CD4 cell count recovers, although often it fails to return to levels seen in healthy individuals. The CD4 count soon after infection with HIV is a strong indicator of the subsequent risk of disease progression: in cases where the CD4 count stabilises at a level below 350, an individual has a higher short-term risk of disease progression.

It is generally assumed that there will be an interval of several years between initial infection with HIV and a fall in CD4 cell count to such levels that the initiation of HIV treatment is warranted. However, there is some evidence in recent years of patients having lower CD4 cell counts shortly after their infection with HIV, and of more rapid disease progression, requiring HIV treatment soon after diagnosis.

US investigators therefore analysed the initial CD4 cell counts of patients recently infected with HIV between 1985 and 2007. The study population was racially diverse and came from HIV treatment centres across the country.

A total of 2 174 people were included in the investigators' analysis. All had had an HIV-negative test result at most 4 years before their diagnosis with HIV. The mean age was 29 years, 96% were men, 45% were African American, 44% white and 11% other ethnicities.

Just over a third (35%) were diagnosed with HIV within a year of a previous negative test result, 41% were diagnosed within 1 - 2 years of testing HIV negative, 17% within 2 - 3 years, and 7% within 3 - 4 years. A CD4 cell measurement was taken within 3 months of HIV diagnosis in 90% of patients.

Changes in initial CD4 cell count were examined in four separate time periods: 1985 - 1990; 1991 - 1995; 1996 - 2001; and 2002 - 2007. Between 1985 and 1990, the mean initial CD4 cell count of individuals recently infected with HIV was 632 cells/mm^3. This fell to a mean of 553 cells/mm^3 for the period 1991 - 1995, and to a mean of 493 cells/mm^3 between 1996 and 2001. The figure then stabilised at a mean of 514 cells/mm^3 between 2002 and 2007.

The fall in initial CD4 cell count for the periods 1985 - 1990 and 1991 - 1995 was highly significant ($p<0.001$), as was the fall between this period and 1996 - 2001 ($p<0.001$).

Further analysis showed that the proportion of individuals with an initial CD4 cell count below 200 cells/mm^3 (an AIDS diagnosis), and 350 cells/mm^3, the point at which it is now recommended to start antiretroviral therapy, increased significantly between 1985 and 2001.

The investigators then conducted statistical analysis to control for possible confounding factors. This showed that compared with the period 1985 - 1990, initial CD4 cell count was 65 cells/mm^3 lower in the period 1991 - 1995 ($p<0.001$), 107 cells/mm^3 lower in the period 1996 - 2001 ($p<0.001$), and 102 cells/mm^3 lower in the period 2002 - 2007 ($p<0.001$).

Similar declines were observed in initial CD4 cell percentage: from 30% in the period 1985 - 1990 to 28% between 1991 and 1995, and 27% in both the later time periods. Adjusted analysis showed that these falls in CD4 cell percentage were significant in all time periods.

Finally the investigators analysed the possible effect of race on their results. They found that in both African-American and white patients initial CD4 cell count declined by a mean of 111 cells/mm^3. 'We observed that initial CD4 cell count among documented HIV seroconverters in the United States significantly decreased during the HIV epidemic,' write the investigators.

This decline reached a plateau after the use of antiretroviral therapy became widespread. The investigators speculate that the fall in initial CD4 cell counts was likely to be because HIV had evolved to become more virulent.

Crum-Cianflone N, *et al. Clin Infect Dis* 2009; 48: 1285-1292.

Weight gain predictive of survival in people on antiretroviral therapy

KELLY SAFREED-HARMON

A study published in the 27 April issue of *AIDS* indicates that weight gain may be a reliable predictor of survival in underweight men and women starting antiretroviral therapy. The finding has broad implications because resource limitations in many developing countries preclude the use of laboratory monitoring to assess treatment effectiveness. If health care providers have some other means of identifying which patients are responding poorly to antiretroviral regimens, they may be able to intervene before those patients become dangerously ill.

The cohort study analysed mortality rates 6 and 12 months after the initiation of antiretroviral therapy. Study participants were being treated in Médecins Sans Frontières (MSF) programmes in Phnom Penh, Cambodia and Homa Bay, Kenya. The most striking finding was that people who had an initial body mass index (BMI) score of 18.5 kg/m^2 or less and experienced weight gains of 10% or less during the first 3 months of antiretroviral therapy were far more likely to die within the next 3 months than people who had comparable initial BMI scores but experienced greater weight gains.

The study population was comprised of 2 451 Cambodian adults and 2 618 Kenyan adults. MSF followed World Health Organization (WHO) recommendations for initiating antiretroviral therapy: people offered antiretrovirals had either a WHO stage 4 condition, a WHO stage 3 condition with a CD4 cell count of less than 350 cells/mm^3, or a CD4 cell count of less than 200 cells/mm^3.

All antiretroviral regimens consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). In

Cambodia, 51% of study participants received 3TC (lamivudine, Epivir), d4T (stavudine, Zerit), and nevirapine (Viramune), while 47% received 3TC, d4T, and efavirenz (Sustiva). In Kenya, 86% of people received the nevirapine-containing regimen, and 9% received the efavirenz-containing regimen.

The study evaluated the prognostic value of weight gain using four categories of initial BMI scores: ≤17 kg/m^2; >17 to ≤18.5 kg/m^2; >18.5 to ≤20 kg/m^2; and >20 kg/m^2. Individuals in the first two categories are considered underweight by international standards. Mortality was analysed in relation to three levels of BMI increase at 3 months and 6 months: ≤5%; >5% to ≤10%; and >10%. Weight gain was found to be predictive of survival for study participants with initial BMI scores in the lower two quartiles, i.e. those who were underweight. People with an initial BMI score of ≤18.5 kg/m^2 and weight gain of ≤5% had a mortality rate ratio (MRR) of 6.3 when compared with those in the same initial BMI category with weight gain of >10% (95% confidence interval (CI) 3.0 - 13.1).

The MRR for people with an initial BMI score of ≤18.5 kg/m^2 and weight gain of >5% to ≤10% was 3.4 when compared with those in the same initial BMI category with weight gain of >10% (95% CI 1.4 - 8.3).

When the researchers compared the prognostic value of weight gain in men and women, they found no significant differences. Nor were there differences between Kenyans and Cambodians, between people who started antiretroviral therapy at different disease stages or CD4 count levels, or between people using different antiretroviral regimens. All of this indicates that tracking weight over time can be an effective strategy in a wide range of antiretroviral recipients.

Weight gain was not predictive of survival for people whose initial BMI score was higher than 18.5 kg/m^2. This somewhat lessens the value of weight monitoring as a clinical management tool. However, given that many people in resource-limited settings do not begin treatment until relatively late in the course of HIV disease, low BMI scores at treatment initiation are not uncommon. Forty-six per cent of Cambodian study participants and almost 40% of Kenyan study participants had BMI scores of 18.5 kg/m^2 or less.

'Weight gain can be of great use in resource-limited settings, especially when decentralization of HIV care is required and access to well-trained physicians is limited,' the authors conclude. They go on to note that three possible reasons for an HIV-positive person's failure to put on weight after initiating antiretroviral therapy are poor medication adherence, opportunistic infections, and insufficient nutritional intake. They advise assessing adherence and providing adherence counselling as warranted.

The authors express particular concern about the importance of screening for tuberculosis (TB) in antiretroviral non-responders, noting: 'The experience from MSF in five countries showed a high incidence of TB (under antiretroviral therapy), and TB remains a leading cause of death in resource-limited settings'.

The authors stress that identifying antiretroviral non-responders by tracking weight should only be regarded as an interim solution. 'Our results should not be interpreted as advocacy for minimal care and monitoring of patients taking ART in developing countries,' they write. 'CD4 cell count and viral load remain the gold standards for patient monitoring, and everything should be done to make these tests available in resource-limited settings.'

Madec Y, *et al. AIDS* 2009; 23: 853-861. Article reproduced with permission from www.aidsmap.com

Financial crisis threatens HIV treatment for 1.7 million

KEITH ALCORN

Up to 1.7 million people in Africa, Eastern Europe, the Caribbean and Asia are at risk of antiretroviral treatment interruption due to the global financial downturn, according to a survey published by the World Bank.

The World Bank report *Averting a Human Crisis During the Global Downturn* was published in advance of the World Bank's spring meeting in Washington DC. It states unequivocally: 'The international community is obligated to continue to support the people it has placed on ART… The international community has made an unambiguous commitment towards universal access to treatment for people with HIV who need it.'

Failure to meet this commitment, the report notes, will call into question the legitimacy of development assistance for health, threaten the gains in health system capacity delivered through HIV treatment programmes and will ultimately result in greater long-term costs due to higher rates of transmission, more TB cases and larger numbers requiring expensive second-line drugs for both HIV and TB.

The World Bank questioned national AIDS programmes in 69 countries in March 2009 and calculated that continuity of treatment could be threatened for around 70% of people currently on treatment in eastern and southern Africa. Around 50% in the Asia-Pacific region, 35% in the Caribbean and 25% in Eastern Europe and Central Asia could also be affected.

The report notes the fragility of financing arrangements for countries largely dependent on external aid for their HIV programmes. Eighteen of 47 countries that provided data said that grants from the Global Fund to Fight AIDS, TB and Malaria end in 2009 or 2010. The Global Fund faces a funding shortfall of $4 billion in 2010, director Professor Michel Kazatchkine said. The Global Fund has postponed its Round 9 funding allocations until November 2009 in order to allow more time to mobilise funding.

Middle-income countries appear less vulnerable, with no countries in Latin America anticipating a reduced ability to pay for antiretroviral treatment during the next year.

Analysing the institutional capacity to make rapid adjustments in financial planning and the fiscal capacity to move domestic funds into treatment at short notice, the World Bank found that all countries would need either a high level of technical support or maintenance of external financing in order to sustain treatment programmes during the next 12 months.

The report emphasises the cost of even minor treatment interruptions: up to 50% of people taking first-line treatment may need a second-line regimen if their treatment is interrupted for more than 15 days, due to the development of drug resistance.

The report also highlights the vulnerability of eastern and southern Africa treatment programmes that are largely dependent on donor aid. Some countries are already experiencing problems: Tanzania has cut its HIV/AIDS budget by 25%, Kenya has reduced its overall health budget, and South Africa anticipates that private sector spending on prevention programmes will decline due to pressure on industry to cut costs.

Thirty-four countries representing 75% of people living with HIV said that they expected prevention programmes to be negatively affected, and national AIDS programmes anticipated greater impact on prevention than treatment, with prevention targeting marginalised groups such as men who have sex with men and injecting drug users at greatest

risk, according to respondents. Eastern Europe and Central Asia were identified as the regions where prevention work with marginalised groups is at greatest risk due to the economic downturn.

The report recommends 'a more rigorous and determined push for efficiency and cost-effectiveness in HIV prevention', together with efforts by donors to identify cash flow problems that might result in treatment interruptions, so that bridging funds can be provided as quickly as possible.

UNAIDS has begun developing an Economic Crisis Impact Assessment Tool that will assist countries in reviewing their epidemics and current responses, and how responses should be revised in the face of the economic crisis.

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Letter to the Editor

A public disgrace

We wish to respond to your Editor's Comment in a recent publication of *CME* as follows:

Let me firstly apologise for the experience you had recently when bringing your employee's husband, Nelson, to Groote Schuur Hospital (GSH).

At the outset let me emphasise that we do strive to maintain services of the highest standard and that, despite the number of challenges that we face, our staff remain committed and dedicated to their patients. As Chief Executive Officer I take complete responsibility for the unhappy experience that you encountered at GSH.

I am sure that you can appreciate that with over 343 689 outpatient visitors, 42 839 inpatient admissions, an average of 24 412 operations and 4 632 births per annum, GSH is a sizeable institution. Unlike large private operations, we cannot simply close our doors to our patients when faced with financial pressures and this we manage within these constraints.

Let me respond to some of the issues that you raise:

Firstly, with the enormous service load that we face, we are not able to always provide timeous and prompt diagnoses. This is particularly evident if patients are waiting for some radiological investigation, a service that is already over-subscribed.

Secondly, let me acknowledge that some of our toilets are in a state of disrepair. We have contracted a private cleaning service for certain areas of the hospital, with the remaining areas being cleaned by our permanent staff.

Although it is not possible to employ dedicated staff to monitor facilities on a 24-hour basis due to limited resources, control measures have been put in place to ensure that frequent inspections are done and that soap and toilet paper are replenished.

The hospital experiences large-scale vandalism, resulting in the theft of plumbing and sanitary ware, as well as items such as soap dispensers and toilet paper. Increased security will be implemented during the current financial year by way of a CCTV camera system, which should go a long way to solving the problem of petty theft, as well as more serious crime.

We have also embarked on a deep cleaning project, focusing on ablution facilities, to ensure that we provide a hygienic environment for patients and the public. Hygiene and infection control are key priorities for the current financial year. The Western Cape Department of Health Quality Assurance Programme has developed a number of measures in order to monitor this objective.

Over the past two years we have embarked on a project to upgrade and replace ablution fixtures and fittings throughout the hospital. This will be an ongoing process in order to establish a standard within the institution.

Thirdly, 90% of our lifts are fully functional and operational. Unfortunately, as a result of vandalism, lifts may be temporarily out of order while they are being repaired. This happens regularly.

Fourthly, the air conditioning airflow in some areas has been reduced due to blocked cooling and heating coils. We are attending to this problem on an ongoing basis.

Lastly, some corridors and other areas in the hospital may well be in need of some paint. Unfortunately our maintenance budget has only allowed us to paint some areas at any point in time. We have spent a considerable amount of money on painting the outside of the hospital and are in the process of repairing the roof as well.

However, despite these challenges and the enormous pressure that our staff face, I still believe that we offer world-class clinical services and that all our staff remain committed to ensuring that the experience of people like Nelson is as humane and caring as possible.

We trust that we have been able to address your concerns satisfactorily and invite you to contact us at any time for any further information.

Kind regards

DR S KARIEM

Chief Executive Officer
Groote Schuur Hospital