AIDS brief

WHO recommends earlier treatment and phase-out of d4T

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Everyone diagnosed with HIV infection should start treatment when their CD4 count falls below 350 cells/mm^3, the World Health Organization (WHO) announced in new recommendations published on 30 November 2009.

The recommendation replaces previous guidelines for low- and middle-income countries, which recommended treatment for people with advanced symptoms of HIV disease, or a CD4 count below 200 without symptoms.

The new guidance also recommends antiretroviral treatment with an efavirenz-based regimen for everyone with TB regardless of CD4 count, and that antiretroviral therapy should be initiated soon after TB treatment.

People with HIV and hepatitis B co-infection who have hepatitis B infection that requires treatment should also receive antiretroviral treatment with a regimen containing tenofovir and either lamivudine (3TC) or emtricitabine (FTC), regardless of CD4 count.

The new guidelines aim to bring treatment in low- and middle-income countries in line with recommendations in Europe, North America and Australia, where earlier treatment has been the norm for several years.

The new guidelines also recommend that all countries should develop plans to phase out the use of stavudine (d4T) in first-line treatment owing to the high frequency of serious toxicities caused by the drug. These toxicities, such as peripheral neuropathy and lipoatrophy, are often irreversible. According to the WHO, d4T is still used in more than half of treatment programmes in low- and middle-income countries.

The new recommendations are accompanied by new guidelines on treatment for women to prevent mother-to-child transmission of HIV, and on infant feeding.

Women who do not need antiretroviral therapy for their own health will now be eligible to receive antiretroviral drugs throughout pregnancy and for the entire duration of breastfeeding.

HIV-positive women will no longer be encouraged to wean their infants early. Instead, the WHO is now recommending 12 months of breastfeeding for HIV-negative infants to ensure that infants have a greater opportunity to benefit from breastfeeding. Although formula feeding is not ruled out, it will be left to individual countries to promote one policy for all women, depending on local circumstances.

Earlier treatment

The WHO issued guidelines for treatment in resource-limited settings in 2003 and updated them in 2006.

The focus of the original guidelines was the scale-up of antiretroviral treatment using a public health approach – a standardised prescription for treatment that could be adopted by any health system, no matter how poorly resourced. The 2003 guidelines emphasised that eligibility for treatment could be determined by the presence of symptoms of advanced HIV disease – so-called WHO stage 4 disease.

Pressure for the WHO to recommend earlier treatment has been growing for several years. A change in the guidelines began to look inevitable in 2009 when the CIPRA HT 001 study in Haiti was halted. This USA-sponsored study was designed to evaluate whether earlier treatment, starting at a CD4 threshold of 350, had a significant effect on reducing death and illness in a low-income setting. The study was halted early after an interim analysis showed a significantly lower rate of deaths in the earlier treatment arm.

In June 2009 Dr Kevin M de Cock, outgoing head of the WHO's HIV department, told delegates at the HIV Implementers' meeting in Windhoek, Namibia: 'The world cannot allow a permanently two-tiered system of global AIDS treatment with late initiation of outmoded drugs reserved for the South.'

The current recommendations, released in advance of publication of the full adult treatment guidelines in early 2010, emphasise the use of CD4 counts to determine eligibility for treatment in place of the previous model.

Treatment should now be initiated when a person's CD4 count falls below 350, regardless of whether symptoms are present or not.

The shift to earlier treatment needs to be supported by a greater investment in laboratory monitoring, and the new guidance recommends that, where available, viral load should be monitored every 6 months and treatment should be switched if viral load has risen above 5 000 copies/ml. However, the WHO states that access to treatment should not be denied if laboratory monitoring is not available.

Although the recommendation of earlier treatment has the potential to greatly increase the numbers in need of treatment, uptake of earlier treatment will be dependent on increasing the uptake of voluntary counselling and testing. Currently the average CD4 count at which people in low- and middle-income countries begin antiretroviral treatment is less than 200. The ART LINC international cohort collaboration reported that the average CD4 count at the time of treatment initiation in 2006 was 122 cells/mm^3 in sub-Saharan Africa, 134 cells/mm^3 in Asia and 197 cells/mm^3 in Latin America.

The influential South African clinician Dr Francois Venter told delegates at the International AIDS Society Conference in July 2009 that, for South Africa, the priority was to get people onto treatment, not earlier treatment, and that despite a big increase in HIV testing in South Africa in recent years, too many patients were being lost from care after diagnosis, only returning when seriously ill.

Country capacity to offer earlier treatment is also questionable, with reports of caps on treatment enrolment in several countries due to a shortage of funds. However, the WHO says that the incremental costs of an additional 1 - 2 years on antiretroviral therapy – the estimated additional time on treatment – may be partly offset by decreased hospital and death costs, increased productivity due to fewer days sick, fewer children orphaned by AIDS, and a decline in new HIV infections as a consequence of suppressed viral load.

An economic analysis of the South African situation, published in 2009, estimated that earlier treatment in line with the new WHO recommendations would cost South Africa $1.5 billion over 5 years if the country's health system was successful in diagnosing and treating everyone eligible for treatment, and $1.1 billion if half of those eligible received treatment.

Phasing out d4T

The WHO is now recommending that national treatment programmes should phase out the use of d4T in first-line treatment owing to the high frequency of serious toxicity. The drug has been the mainstay of antiretroviral treatment scale-up in resource-limited settings due to its low cost and its availability in cheap, generic fixed-dose combinations.

Instead, treatment programmes should use tenofovir or zidovudine (AZT). However, both these drugs are more expensive than d4T, and in the case of tenofovir, only available in a 3-drug fixed-dose combination with efavirenz, also more expensive than the other mainstay of treatment scale-up, nevirapine. The WHO acknowledged in its statement that implementation of the recommendations will depend on national circumstances, resources and priorities.

ART LINC Cohort Collaboration. Antiretroviral therapy in resource-limited settings 1996 to 2006: patient characteristics, treatment regimens and monitoring in sub-Saharan Africa, Asia and Latin America. *Trop Med Int Health* 2008; 13(7): 870-879.

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BRIDGET FARHAM

Single Suture

Risk of gastric cancer increased in the overweight or obese

Do body weight and obesity have anything to do with the risk of stomach cancer? A Chinese meta-analysis of data of over 3 million people and nearly 9 500 cases of gastric cancer concludes that overall excess body weight is associated with an increased risk of gastric cancer (odds ratio 1.22, 95% confidence interval 1.06 - 1.41). The strength of the association also increased with increasing body mass index.

Yang P, *et al. Eur J Cancer* 2009; 45: 2867-2873.

Single Suture

Evening breastfeeding best for a good night's sleep

Mothers who use expressed breastmilk through the night must be careful about when they express the milk, according to Cristina Sánchez at the University of Extremadura in Badajoz, Spain. The naturally occurring chemicals in human breastmilk that cause sleepiness are most concentrated in milk expressed at night, so breastmilk pumped and bottled during the day may not help babies fall asleep if given to them at night.

The sedatives are nucleotides and several have been implicated in the processes of sleep. The chemicals had already been found in breastmilk, the concentrations increasing in the first few weeks after birth, so it seemed likely that they had a developmental function. It now looks as though they also help babies to fall asleep.

Sánchez and colleagues looked at the concentration of 5'UMP, 5'AMP and 5'GMP – the 3 nucleotides most strongly associated with sleep and sedation – in the breastmilk of 30 healthy mothers who had been breastfeeding for at least 3 months. Samples of milk were collected before each feed over 24 hours, with between 6 and 8 samples per mother.

The highest concentrations of 5'AMP were found in the evenings, while levels of 5'UMP and 5'GMP increased during the course of the night. These sedatives were found at much lower concentrations in milk expressed during the day. Sánchez suggests that 5'AMP in breastmilk may be fuelling the neurotransmitted GABA and that 5'GMP is involved in the stimulation of melatonin. 5'UMP is known to encourage both REM and non-REM sleep.

The researchers also created a 'night-time milk' by adding 5'AMP and 5'UMP to standard formula milk. Infants receiving this milk between 18h00 and 06h00, and normal milk during the day, fell asleep faster and spent longer asleep than when they drank standard formula milk all the time.

New Scientist 10 October 2009: 13.