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New WHO treatment guidelines

By Theo Smart

WHO recommends earlier treatment and phase-out of d4T

By Keith Alcorn

Everyone diagnosed with HIV infection should start treatment when their CD4 count falls below 350 cells/mm³, the World Health Organization announced in new recommendations published on November 30th 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, with antiretroviral therapy to be initiated soon after TB treatment.

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

The [new guidance](#) aims to bring treatment practice in low and middle-income countries into 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 d4T (stavudine) in first-line treatment due to the high frequency of serious toxicities caused by the drug. These toxicities, such as peripheral neuropathy (nerve damage) and lipodystrophy (fat loss) are often irreversible. According to WHO d4T is still used by more than half of treatment programmes in low and middle-income countries.

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

Women who do not need ART 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, WHO is now recommending 12 months of breastfeeding for HIV-negative infants, in order to ensure that infants have a greater opportunity to benefit from breastfeeding. Although formula feeding is not ruled, it will be left to individual countries to promote one policy for all women, depending on local circumstances.

Earlier treatment

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 by 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 WHO to recommend earlier treatment has been growing for several years. A change in the guidelines began to look inevitable earlier this year when [the CIPRA HT 001 study in Haiti](#) was halted. This US-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 Dr Kevin M de Cock, outgoing head of the WHO's HIV department told the 2009 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."

Today's recommendations, released in advance of publication of the full adult treatment guidelines in early 2010, emphasise the use of CD4 counts in order 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 six months and treatment should be switched if viral load has risen above 5,000 copies/ml. However 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. At present 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/mm³ in sub-Saharan Africa, 134 cells/mm³ in Asia and 197 cells/mm³ in Latin America.

The influential South African clinician Dr Francois Venter [told the International AIDS Society conference in July](#) 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 WHO says that the incremental costs of an additional one to two years on ART – 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 drop in new HIV infections as a consequence of suppressed viral load.

An economic analysis of the South African situation, [published earlier this year](#), estimated that earlier treatment in line with the new WHO recommendations would cost South Africa \$1.5 billion over five 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

WHO is now recommending that national treatment programmes should phase out the use of d4T in first-line treatment due 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 three-drug fixed-dose combination with efavirenz, also more expensive than the other mainstay of treatment scale-up, nevirapine. WHO acknowledged in its statement today that implementation of the recommendations will depend on national circumstances, resources and priorities.

Further information

The difficulties facing national treatment programmes in phasing out d4T and shifting to earlier treatment were reviewed in a [June 2008 edition of HIV & AIDS Treatment in Practice](#), NAM's electronic newsletter on HIV treatment in resource-limited settings, and in a [June 2007 news report from the HIV Implementers' meeting in Rwanda](#).

Reference

World Health Organization. *Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents*. November 30, 2009. Download at <http://www.who.int/hiv/pub/arv/advice/en/index.html>.

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* 13(7):870-9, 2008.

New WHO guidelines on PMTCT and infant feeding

By Carole Leach-Lemens

New recommendations from the World Health Organization (WHO) for preventing mother-to-child transmission (PMTCT) have the potential to improve child survival and the mother's own health, to reduce mother-to-child transmission risk to five percent or lower and virtually eliminate paediatric HIV infection, WHO said today.

The recommendations represent significant shifts in practice in several areas. The key recommendations are:

- Antiretroviral therapy for all HIV-positive pregnant women with a CD4 count below 350 or WHO stage 3 or 4 HIV disease, with treatment to begin without delay using a backbone of AZT and 3TC or tenofovir and either 3TC or FTC.
- Longer provision of antiretroviral prophylaxis for HIV-positive pregnant women who are not in need of ART for their own health
- Where mothers are receiving ART for their own health, infants should receive prophylaxis with nevirapine for six weeks after birth if the mother is breastfeeding, and prophylaxis with either nevirapine or AZT for 6 weeks if the mother is not breastfeeding.
- For the first time there is enough evidence for WHO to support giving antiretroviral therapy to the mother or child throughout the breastfeeding period, with the recommendation that breastfeeding and prophylaxis should continue until 12 months of age if the infant is either HIV-negative or of unknown status.

- Where mother and infant are both HIV-positive, breastfeeding should be encouraged for at least the first two years of life, in line with recommendations for the general population.

"In the new recommendations we are sending a clear message that breastfeeding is a good option for every baby, even those with HIV-positive mothers, when they have access to antiretrovirals," said Daisy Mafubelu, WHO's Assistant Director General for Family and Community Health.

The guidelines offer guidance to countries on how to reduce HIV transmission from mother-to-child through more effective treatment and prevention regimens.

First issued in 2000 and revised in 2004 and 2006 the PMTCT antiretroviral guidelines recommend the delivery of simple, standard and effective regimens on a large scale in all settings.

The 2006 guidelines highlighted the importance of lifelong antiretroviral treatment for eligible HIV-positive pregnant women for their own health and their children. In addition combination antiretroviral prophylaxis replaced single-dose nevirapine. These guidelines serve as the technical backbone for rapid PMTCT scale-up, in particular in sub-Saharan Africa where more than 90 percent of HIV-positive pregnant women live.

An estimated 21% of pregnant women received an HIV test in 2008 and 45% received drugs to prevent mother to child transmission, of whom around one-third received single-dose nevirapine, the least effective form of preventive treatment. Only one-third of those who tested positive were assessed for eligibility for antiretroviral treatment for their own health.

With an estimated 1.4 million pregnant women in low- and middle-income countries living with HIV in 2008 much more needs to be done to scale up HIV testing and counselling and PMTCT including integration of these services into strengthened maternal and child health programmes.

The 2009 guidelines

The new guidelines recommend lifelong antiretroviral treatment for all pregnant women with serious or advanced disease or with a CD4 count at or below 350 regardless of symptoms. Evidence suggests that this could prevent 75% of all mother-to-child transmission while also providing the best available treatment for the mother's health, says WHO, in addition to providing protection during the breastfeeding period. It is consistent with the new adult ART recommendations.

In women who do not need antiretroviral therapy for their own health (CD4 count above 350) antiretroviral therapy is to start earlier in the pregnancy, at 14 weeks or as soon as possible thereafter and should continue through the end of the breastfeeding period. This change reflects evidence from clinical trials showing the efficacy of antiretrovirals in preventing transmission of HIV to the infant while breastfeeding. In 2006 guidelines recommended starting ART at 28 weeks with a basic daily regimen of zidovudine (AZT) and single-dose nevirapine during labour and delivery, as well as infant prophylaxis for one week after birth.

The 2009 guidelines offer two options:

- Daily AZT for the mother during pregnancy, single dose nevirapine at the onset of labour, AZT/3TC during labour and for 7 days post-partum. If a mother has taken AZT for at least four weeks prior to delivery AZT/3TC and single-dose nevirapine can be omitted. Infant prophylaxis with nevirapine or AZT should be continued until the end of the breastfeeding period or for six weeks after birth in non-breastfeeding infants.

Or

- A three-drug regimen for the mother taken during pregnancy and throughout the breastfeeding period, as well as infant prophylaxis as in option A. The recommended regimens are AZT/3TC plus efavirenz, abacavir or lopinavir/ritonavir (Kaletra/Aluvia).

New advice on infant feeding

WHO's international expert review panel decided that there is now enough evidence for WHO to recommend antiretroviral treatment during breastfeeding.

Breastfeeding is to continue until the infant is 12 months old in HIV-exposed but uninfected infants, and those of unknown HIV status, as long as the HIV-positive mother or baby is taking antiretrovirals during this time.

While most babies of HIV-positive women in resource-rich settings are given formula feed from birth in order to prevent transmission through breastfeeding after delivery, in resource-limited settings safe replacement feeding has not been a viable option.

Depending on available interventions to prevent HIV transmission through pregnancy and delivery, breastfeeding has been responsible for between 30-60% of all HIV infections in children. Yet children who do not breastfeed are up to six times more likely to die from diarrhoea, malnutrition or pneumonia.

Mothers are faced with choosing between the benefits of breastfeeding but exposing their children to the risk of HIV transmission or not breastfeeding and increasing the child's risk of death from other diseases.

There are two choices for HIV-positive women who breastfeed and are not taking ART:

- If a woman received zidovudine during pregnancy, daily nevirapine is recommended for her child from birth until the end of the breastfeeding period.

Or

- If a woman received a three-drug regimen during pregnancy, a continued regimen of three-drug prophylaxis is recommended for the mother until the end of the breastfeeding period.

Recommendations for infant feeding practices in the first 24 months of life:

- Mothers known to be HIV-infected (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first six months of life, introducing appropriate complementary foods after that, and continue breastfeeding for the first 12 months of life. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided.
- If infants and young children are known to be HIV-infected mothers are strongly encouraged to exclusively breastfeed for the first six months of life and continue breastfeeding as recommended for the general population, that is up to two years and beyond.

National authorities are advised to choose one national policy, based on local circumstances and health system capacity: either to counsel and support mothers infected with HIV to breastfeed and receive ART interventions or to avoid all breastfeeding, as the strategy that will give the best chance of remaining uninfected and alive. WHO is developing guidelines to assist countries in this decision-making process. As in 2006 the recommendations reaffirm

the call for agencies to invest in improved infant and young child nutrition.

In countries not affected by HIV it is estimated that improved infant feeding practices can reduce child mortality by up to 19 percent. The reduction in child mortality could be significantly greater in populations affected by HIV if improved feeding practices can be promoted throughout the population, not just among HIV-positive mothers, WHO says.

Weak health infrastructure, lack of human resources, limited management capacity as well as lack of funding and support for PMTCT still challenge scale-up and guideline implementation.

WHO suggests that successful implementation of the new guidelines will depend on:

- Universal voluntary HIV testing and counselling for pregnant women
- Availability of CD4 testing and ART at primary care level and antenatal facilities where most maternal-child health care takes place, and not just in specialized clinics
- Improved follow-up of pregnant women antenatal and of mothers and HIV-exposed infants after birth
- Ability to provide prophylaxis to the mother or baby throughout breastfeeding, as well as infant feeding counselling and support
- Appropriately trained staff.

The full guidelines are due to be published early in 2010.

References

World Health Organization. *Rapid advice: use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants*. November 30, 2009. Download at <http://www.who.int/hiv/pub/mtct/advice/en/index.html>

World Health Organization. *Rapid advice: revised WHO principles and recommendations on infant feeding in the context of HIV*. November 30, 2009. Download at http://www.who.int/child_adolescent_health/documents/9789241598873/en/index.html

South Africa announces policy shift to earlier treatment

By Keith Alcorn

South Africa's President Jacob Zuma announced on December 1st that all HIV-positive pregnant women and TB patients with CD4 counts below 350 will qualify for immediate antiretroviral treatment from April 2010, and all children under one year of age will be provided with immediate ART if they test positive.

President Zuma also encouraged all South Africans to get tested for HIV, and told South Africans, "I am making arrangements for my own test. I have taken HIV tests before, and I know my status. I will do another test soon as part of this new campaign. I urge you to start planning for your own tests."

He said that the South African government will launch a "massive" testing campaign shortly, as part of a break with previous mixed messages about HIV from senior politicians such as President Thabo Mbeki and Health Minister Manto Tshabalala-Msimang.

"Let today be the dawn of a new era," he said. "Let there be no more shame, no more blame, no more discrimination and no more stigma."

"Let the politicisation and endless debates about HIV and AIDS stop."

"Let this be the start of an era of openness, of taking personal responsibility, and of working together in unity to prevent HIV infections and to deal with its impact."

The South African announcement on earlier treatment follows a recommendation issued on November 30th by the World Health Organization, which urged national governments to move to earlier treatment as quickly as possible.

WHO recommended that all people diagnosed with HIV infection should start treatment when their CD4 count falls below 350. South Africa's decision to prioritise pregnant women and people with TB/HIV coinfection is a compromise designed to target treatment to the groups where treatment may have the greatest impact on new infections and deaths.

"All patients with both TB and HIV will get treatment with antiretrovirals if their CD4 count is 350 or less," Zuma announced today in a World AIDS Day speech screened live on national television.

"At present treatment is available when the CD4 count is less than 200. TB and HIV/AIDS will now be treated under one roof. This policy change will address early reported deaths arising from undetected TB infection among those who are infected with HIV."

"All pregnant HIV positive women with a CD4 count of 350 or with symptoms regardless of CD4 count will have access to treatment. At present HIV positive pregnant women are eligible for treatment if their CD4 count is less than 200."

"All children under one year of age will get treatment if they test positive. Initiating treatment will therefore not be determined by the level of CD4 cells."

The US government has pledged an additional \$120 million over two years through PEPFAR to treat additional patients, but the South African government has issued no assessment of the additional numbers who need treatment, or the additional cost.

AIDS-free generation of children achievable, says UN report

By Carole Leach-Lemens

A generation of children free from AIDS is possible, according to the *Children and AIDS, Fourth Stocktaking Report* released on November 30th by UNICEF in partnership with the joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization (WHO) and the United Nations Population Fund (UNFPA). However, the authors note the world is not yet on track to meet targets for prevention, treatment, care and support.

Issuing a call for action they urge that in a climate of economic uncertainty long-term targets are kept in mind and short-term commitments are honoured if women, children and young people are to have opportunities to live and thrive in a world free of AIDS.

"Wise investment in HIV and AIDS at the country level will require us to 'know the epidemic', how to respond appropriately and the associated costs of that response, and how that response is affecting the health and wellbeing of women and children," says UNICEF.

In 2005 UNICEF, UNAIDS and other partners launched Unite for Children, Unite against AIDS to focus attention and resources dedicated to putting children at the heart of the global response. The partnership has published a series of annual stocktaking reports to track progress towards the goal of universal access to prevention, treatment and care.

Interventions including early infant diagnosis and antiretroviral therapy for the prevention of mother-to-child transmission are now

a part of the global response and have helped save and improve lives. Yet progress remains uneven revealing gaps in service coverage and inequities in access.

The report highlights the need for systems strengthening – health, political, legal and social welfare – linking them with communities to improve delivery and uptake of HIV/AIDS interventions.

This fourth annual report examines progress made in the global response for children in four programme areas known as the 'Four Ps':

- Preventing mother-to-child transmission
- Paediatric HIV care and treatment
- Preventing HIV infection among adolescents and young people
- Protecting and supporting children affected by HIV and AIDS

According to UNICEF \$5.9 billion annually is a best estimate of the resources needed to adequately address the requirements of women, children and young people to meet the targets of the Four Ps.

Progress towards universal access goals, in the 20th anniversary year of the Convention on the Rights of the Child, is examined through the perspective of a standard of care and treatment for all that ensures the most-at-risk and vulnerable children and families do not fall through the cracks.

Prevention of mother-to-child transmission

Nineteen (of 192 United Nations member states) countries reached the United Nations General Assembly Special Session on HIV/AIDS (UNGASS) goal of reaching 80 percent of pregnant women living with HIV with antiretroviral therapy to prevent transmission of HIV to their infants in 2008.

In 2008 45 per cent of HIV-positive pregnant women received antiretroviral drugs to prevent transmission of the virus to their infants. While the number of women reached has almost doubled since 2006 only 21 per cent of the estimated pregnant women living in low- and middle-income countries were tested for HIV in 2008.

On average in low- and middle-income countries 32 per cent of infants born to HIV-positive mothers were given antiretroviral prophylaxis for PMTCT at birth, up from 20 per cent in 2007 and 18 per cent in 2006. This ranges from a low of 10 percent in West and Central Africa, 20 per cent in South Asia, 40% in Eastern and Southern Africa to 54% in Latin America and the Caribbean.

While some progress has been made, few pregnant women are taking ART for their own health and the majority of pregnant women and children do not have access to basic PMTCT services.

Evidence-based strategic approaches for PMTCT scale-up that have proved successful in resource-limited settings include: Decentralisation, health systems strengthening and integration within maternal, newborn and child health services, scaling-up innovative service delivery, (for example mobile technology and motor-bikes) and making community-based interventions an integral part of national scale-up plans.

Paediatric HIV care and treatment

In 2008 approximately 275,000 (38%) of children under 15 in need of antiretroviral treatment received it. Early testing and immediate treatment in infants is critical, because evidence suggests AIDS-related deaths are at their highest at two to three months of age. However, improved access to early infant diagnosis viral DNA

testing of dried blood spots does not necessarily mean access to life-saving treatment. A Clinton Foundation study in eight countries revealed an estimated 53 per cent loss-to-follow-up after testing positive among mothers and children (following birth).

Cotrimoxazole prophylaxis is a life-saving intervention when started in HIV-exposed children within two months of age, and is highly cost-effective. However, coverage in low- and middle-income countries in 2008 was only 8 per cent, up from 4 per cent in 2007.

Preventing infections among adolescents and young people

Young people (aged 15-24) represent 45 percent of all new adult infections. Of the estimated 4.9 million young people living with HIV 60 percent live in Eastern and Southern Africa while 23 percent live in West and Central Africa. Young women are especially vulnerable when understood within a social, cultural and economic context that places them at high risk of HIV exposure. They account for close to 75% of infections in young people in sub-Saharan Africa. In South Asia, Latin America and the Caribbean more young men than young women are becoming infected, due to the concentrated nature of HIV epidemics taking place largely among injecting drug users and men who have sex with men.

In all regions gender discrimination and gender-based violence limit access to services and reduce people's ability to make choices in risk reduction.

Men who have sex with men, sex workers and injecting drug users all face multiple barriers in accessing services.

Knowing the epidemic at the local level to be able to design and tailor interventions that address behaviours that marginalise and put adolescents at risk for infection is fundamental. Although girls who attend school for more years are at lower risk of HIV infection, evidence on how to use schools effectively to reduce HIV risk within a national framework is still lacking.

Protection, care and support for children affected by HIV and AIDS

A median of 12 percent of households caring for orphans or vulnerable children in 2008 received any kind of basic external support. The current economic climate further adds to the additional stresses that poverty brings to the well-being of children affected by HIV.

The report highlights how child-sensitive social protection is a key intervention to reaching children affected by AIDS, and includes: social transfers (cash and in-kind transfers and vouchers), social insurance, social services and social policies and legislation designed to be AIDS sensitive.

Programme monitoring and evaluation

Evidence-based programmes that show what works (or does not) and how to make improvements are key to scale-up. Monitoring and evaluation of PMTCT and paediatric HIV programmes must keep up with advances in science and programming.

Call to action

For women, children and young people to have the opportunities to live and thrive in a world free of AIDS there are ten priorities, UNICEF says:

- Accelerate the scale-up of PMTCT services and early infant diagnosis to contribute to the elimination of HIV transmission to young children.
- Continually seek out new evidence to inform HIV prevention.
- Support and empower adolescents, particularly girls, to identify and respond to their own vulnerabilities.
- Protect the rights of adolescents and young people living with HIV to receive good quality support and services.
- Ensure that adolescents who are in situations of the greatest risk are reached by HIV prevention, treatment, care and support services.
- Make sexual violence against girls and women socially unacceptable.
- Scale-up child-sensitive social protection, a necessary part of the response for children affected by AIDS.
- Strengthen the community capacity to respond to the needs of children affected by AIDS by preventing the separation of families and improving the quality of alternative care.
- Strengthen whole systems so that gains made on behalf of women and children affected by AIDS can be extended and sustained.
- Improve data gathering and analysis to achieve results for children, and identify gaps in equitable coverage of and access to services.

Further information

The Fourth Stocktaking Report can be downloaded at <http://www.aidsmap.com/en/news/www.uniteforchildren.org>

Reference

UNICEF. *Unite for Children, Unite against AIDS. Children and AIDS: The fourth stocktaking report, November 2009.*