

CD4: the bar is raised

WHO moves to raise the indicator point for the commencement of ARV treatments, and moves towards less toxic drug options

The World Health Organization (WHO) is revising guidelines on antiretroviral therapy (ART) for adults and adolescents. While the full guidelines are expected in early 2010, key recommendations of the new guidelines were released on 30 November 2009 (see Rapid advice document: http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf).

Key 2009 recommendations: ART

1. Earlier diagnosis and treatment of HIV in the interest of a prolonged and healthier life.
2. Greater use of more patient-friendly treatment regimens.
3. Expanded laboratory testing to improve the quality of HIV treatment and care.

Background

WHO has a mandate to define global health norms and standards and to help countries adopt and adapt these recommendations to their national circumstances.

WHO's ART guidelines for adults and adolescents are intended to optimise patient care and survival. They recommend the delivery of simple, standard, quality interventions at a large scale, including in resource-limited settings.

The ART guidelines, first published in 2002, were summarised and simplified in 2003 and updated in 2006. They have been critical to the enormous progress made towards universal access to HIV treatment and care.

However, national ART programmes are facing significant challenges as most people start treatment too late, often due to late HIV diagnosis. This leads to high rates of early mortality and associated opportunistic diseases, such as tuberculosis (TB), and undermines the dramatic gains in scaling up access to treatment.

Need for updated guidelines

Significant evidence and experience on when to initiate ART and what drug regimens to use have accumulated since the 2006

revision of the guidelines.

Most high-income countries have revised their national ART guidelines to recommend an earlier start to treatment and to avoid the use of Stavudine (d4T), which is still widely used in first-line therapy in low-income countries. Stavudine use has well recognised long-term toxicity problems that are not reversible.

WHO is recommending that all governments adopt national policy guidelines that promote an earlier start to treatment and transition to less toxic first-line drugs. Implementation of the recommendations will depend on national circumstances, resources and priorities.

Main revisions

Eligibility for treatment

The best time to start ART is before patients become unwell or develop their first opportunistic infection. The best method to determine when to start treatment is through CD4 testing, which measures the strength of the immune system.

The 2006 guidelines recommended that ART be started for all patients with advanced clinical disease and/or a CD4 count of 200 cells/mm³ or less.

The 2009 recommendations promote earlier treatment for all patients, when their CD4 count falls to 350 cells/mm³ or less, regardless of symptoms.



Pharmacy output will change if new guidelines are implemented

WHO has issued revised recommendations on when to start treatment for specific populations, including HIV-positive pregnant women and HIV-positive people co-infected with either TB or Hepatitis B.

Treatment regimens

Stavudine has long-term, cumulative, and non-reversible toxicities such as peripheral neuropathy (disorder of peripheral nerves characterized by numbness, weakness and burning pain of hands and feet) and lipoatrophy (the loss of fat from specific parts of the body).

The 2006 guidelines recognized the critical role of Stavudine (d4T)-containing regimens due to its low cost, limited need for laboratory monitoring, initial tolerability and widespread availability. However, they recommended that countries plan to move away from d4T.

The 2009 recommendations propose that countries progressively phase out the use of Stavudine as a preferred first-line therapy option and move to less toxic alternatives such as Zidovudine (AZT) and Tenofovir (TDF).

According to WHO surveys, the use of Stavudine is decreasing globally, but it is still the main first-line therapy option used by more than half of programmes in low- and middle-income countries. The guidelines therefore recommend a phased approach to this transition. WHO will help countries draw up plans to phase out Stavudine safely without jeopardizing sustainability and access to treatment.

Role of laboratory testing

There are well recognized limitations to relying only on clinical monitoring¹ to determine when people need to start ART and when they are beginning to fail to respond to their treatment regimen.

The 2009 recommendations outline an expanded role for laboratory monitoring, including both CD4 testing and viral load monitoring², to improve the quality of HIV treatment and care. They promote greater access to CD4 testing and the strategic introduction of viral load monitoring. Access to ART must not be denied if these monitoring tests are not yet available.

1. Clinical monitoring: The monitoring of a patient's health by a trained health professional. This typically involves taking a patient's medical history on a regular basis and conducting routine clinical examinations.
2. Viral load monitoring: Measuring the concentration of HIV in the bloodstream.

Benefits

The new recommendations are based on a solid body of evidence indicating that rates of death, morbidity and HIV and TB transmission are all reduced by starting treatment earlier. This prolongs and improves quality of life.

An earlier start to treatment reduces a person's viral load much earlier in the course of their HIV infection, and thereby reduces the risk of onward HIV transmission and could potentially avert a significant number of new HIV infections.

Earlier treatment would boost the immune system,

making it less likely that the patient falls sick with TB and other opportunistic diseases which prey on weakened immune systems. This would benefit both the individual concerned and help protect the wider community against the risk of infectious TB.

The prospect of earlier treatment could also act as an incentive for more people to undergo voluntary counseling and testing without waiting to develop symptoms and fall sick.

The phasing out of Stavudine would enable new and existing patients to avoid disabling and disfiguring side-effects and reduce the costs of managing these toxicities.

Expanding CD4 testing will enable people to access earlier treatment, before they become unwell, and it is critical to identifying pregnant women who need ART. Wide-scale access to CD4 testing among HIV-positive pregnant women would help to prevent the bulk of mother-to-child transmission of HIV (see also Rapid advice on PMTCT).

Challenges

The main challenge is to increase access to treatment in low- and middle-income countries and to encourage people to receive voluntary HIV testing and counselling before they have any symptoms. Currently, many HIV positive people are waiting too long before they seek treatment, usually when their CD4 threshold falls below 200 cells/mm³.

Raising the CD4 threshold to 350 cells/mm³ may mean an average 1–2 years' additional exposure to ART, prompting some concern about the risk of ART toxicity.

By choosing a limited number of treatment regimens that suit the majority of people in need of ART, governments can achieve economies of scale through the purchase of larger quantities of a smaller number of drugs.

It is unclear if HIV-positive patients who feel well will be willing start ART and whether they will have more difficulty adhering to treatment than those who are showing symptoms. However, the prospect of a prolonged and healthier life could act as inducement for earlier treatment.

The WHO ART guidelines committee concluded that the benefits of adopting these new treatment recommendations outweighed the potential risks.

The review process

WHO has a guideline review committee which oversees the development, approval and updating of WHO recommendations, according to strict procedures specified by WHO's handbook for guideline development.

Dissemination and implementation

WHO, in collaboration with key partners, will provide technical support to the highest burden countries to adapt and adopt the revised policy guidance. It will draw up transition and adaptation guides to help countries move to higher treatment thresholds and less toxic treatment regimes according to national circumstances, without jeopardizing the goal of access to universal and equitable coverage.

Preventing mother-to-child transmission

New guidelines urge ARV treatment to commence 14-weeks into pregnancy

The World Health Organization (WHO) is revising its guidelines on the use of antiretroviral (ARV) drugs for the prevention of mother-to-child transmission of HIV (PMTCT). Key recommendations of the new guidelines were released on 30 November 2009 (see Rapid advice document: http://www.who.int/hiv/pub/mtct/rapid_advice_mtct.pdf). The full guidelines are expected in early 2010.

Key 2009 recommendations: PMTCT

1. Earlier antiretroviral therapy (ART)¹ for a larger group of HIV-positive pregnant women to benefit both the health of the mother and prevent HIV transmission to her child during pregnancy.
2. Longer provision of antiretroviral (ARV) prophylaxis² for HIV-positive pregnant women with relatively strong immune systems who do not need ART for their own health. This would reduce the risk of HIV transmission from mother to child.
3. Provision of ARVs to the mother or child to reduce the risk of HIV transmission during the breastfeeding period. For the first time, there is enough evidence for WHO to recommend ARVs while breastfeeding. The PMTCT recommendations refer to two key approaches:
 1. Lifelong ART for HIV-positive women in need of treatment.
 2. Prophylaxis, or the short-term provision of ARVs, to prevent HIV transmission from mother to child.

Background

WHO has a mandate to define global health norms and standards and to help countries adopt and adapt these recommendations to their national circumstances.

The PMTCT ARV Guidelines, first issued in 2000, were revised in 2004 and again in 2006. They recommend the delivery of simple, standard and effective regimens at a large scale, even in resource-limited settings.

The 2006 guidelines have formed the technical backbone of the rapid scale-up in PMTCT services, especially in high burden countries in sub-Saharan Africa, where more than 90% of HIV-positive pregnant women reside.

However, much more needs to be done to accelerate the scale-up of HIV testing and counselling and PMTCT, and to integrate these services with strengthened maternal, newborn and child health programmes.

Need for updated guidelines

Significant evidence and experience have accumulated since the 2006 revision of the guidelines, especially

with regard to:

- when women should receive treatment for their own health and to reduce the risk of HIV transmission;
- the benefits of starting ARV prophylaxis earlier during pregnancy with either one or three drugs;
- evidence that ARV prophylaxis for mothers or infants reduces significantly the risk of transmission through breastfeeding.

Implementation of the recommendations and new country guidelines will depend on national circumstances, resources and priorities.

Main revisions:

Eligibility for treatment

The best method to determine when to start treatment is through CD4 testing, which measures the strength of the immune system.



The 2006 guidelines recommended starting lifelong ART for pregnant women with a CD4 count at or below 200 cells/mm³, usually the stage at which the immune system is no longer strong enough to prevent opportunistic diseases.

The 2009 recommendations promote starting lifelong ART for all pregnant women with severe or advanced clinical disease, or with a CD4 count at or below 350 cells/mm³, regardless of symptoms.

Clinical trials and additional data suggest that treating pregnant women with a CD4 count at or below 350 cells/mm³ could prevent at least 75% of all mother-to-child transmission while also providing the best available treatment for the mother's health. ART will also provide protection during the breastfeeding period.

ARV prophylaxis during pregnancy

HIV-positive pregnant women who are not eligible or are not receiving ART (lifelong treatment) should be given ARVs as prophylaxis to prevent transmission to their children.

The 2006 guidelines proposed starting ARV prophylaxis in the third trimester (28 weeks) of

pregnancy. They recommended a basic regimen of daily zidovudine (AZT) and single-dose nevirapine at labour and delivery, as well as infant prophylaxis for one week after birth.

The 2009 recommendations include two options, both of which should start earlier in pregnancy, at 14 weeks or as soon as possible thereafter.

1. Daily AZT for the mother and infant prophylaxis for six weeks after birth. Infant prophylaxis should be continued until the end of the breastfeeding period.

OR

2. A three-drug regimen for the mother taken during pregnancy and throughout the breastfeeding period, as well as infant prophylaxis for six weeks after birth.

ARV prophylaxis during breastfeeding

In most developed countries, babies of HIV-positive mothers are given infant formula from birth in order to prevent postpartum transmission through breastfeeding. But in many countries, both health services and individual mothers have not been able to adequately support and provide safe replacement feeding. Mothers have faced the dilemma of either giving their babies all the benefits of breastfeeding but exposing them to the risk of HIV infection, or avoiding all breastfeeding and increasing the risk of death from diarrhoea and malnutrition.

At the time of the 2006 guidelines, there were insufficient data supporting the use of ARVs to prevent HIV transmission from mother to baby during breastfeeding. Since then, several clinical trials have shown the efficacy and acceptability of prophylaxis either to the mother or to the infant during breastfeeding.

The 2009 recommendations reflect this exciting breakthrough. They provide two alternative options for HIV-positive women who breastfeed and are not taking ART:

1. If a woman received AZT during pregnancy, daily nevirapine is recommended for her child from

birth until the end of the breastfeeding period. OR
2. 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.

Benefits

The new recommendations offer the potential for all countries to virtually eliminate paediatric HIV. Combined with improved infant feeding practices, the recommendations can help to reduce both child mortality and new HIV infections.

An estimated 2.1 million children under the age of 15 were living with HIV in 2008, according to the latest available data, and there were some 430 000 new HIV infections in children. Nearly all of these new infections in children could have been prevented with effective PMTCT interventions.

PMTCT can also act as a gateway to improved reproductive, maternal and child health services at primary level and, in turn, bolster progress towards achieving the health-related Millennium Development Goals of reducing under-five mortality rates by two thirds, decreasing maternal mortality rates by three quarters, and halting and reversing the spread of HIV/AIDS by 2015.

Challenges

The major challenges in scaling-up national PMTCT services and implementing the new recommendations are weak health infrastructure, limited human resources, limited management capacity, and limited funding and support for PMTCT. However there are many hopeful signs that PMTCT programmes now have greater priority both at the national and international level.

Successful implementation of the new guidelines will depend on:

- universal, voluntary HIV testing and counselling for pregnant women;
- availability of CD4 testing and ARVs 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 antenatally 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 review process

WHO has a guideline review committee which oversees the development, approval and updating of WHO recommendations, according to strict procedures specified by WHO's handbook for guideline development.

Dissemination and implementation

WHO, in collaboration with key partners, will provide technical support to all regions and additional support to high-burden countries to adapt and adopt the revised policy guidance. The full guidelines will be published in both English and French and will then be translated and published in at least three other languages.