

KEY MESSAGES

NEW WHO RECOMMENDATIONS: Antiretroviral therapy for adults and adolescents

The World Health Organization (WHO) is revising its guidelines on antiretroviral therapy (ART) for adults and adolescents. Key recommendations of the new guidelines will be released on 30 November 2009 (see *Rapid advice* document). The full guidelines are expected in early 2010.

The revised ART recommendations are a reference for best clinical practice and will help countries set their own national standards for HIV treatment and care.

WHO is also revising its guidelines on preventing mother-to-child transmission of HIV and infant feeding in the context of HIV. All three guidelines are being updated in a harmonized fashion.

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. However, access to laboratory tests should not be a prerequisite for treatment.

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 optimize 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 summarized 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.

According to the WHO/UNICEF/UNAIDS *Towards universal access* progress report (2009), more than 4 million people had access to antiretroviral therapy in low- and middle-income countries at the end of 2008, representing a tenfold increase over five years. Of the estimated 9.5 million people in need of treatment in 2008, 42% had access, up from 33% in 2007. Intensified political commitment and focused international financial support contributed to impressive progress in sub-Saharan Africa, which accounts for two-thirds of the estimated 33.4 million HIV infections.

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 recognized 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.

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. Please see the *Rapid advice* document for details.

TREATMENT REGIMENS

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).

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 lipodystrophy (the loss of fat from specific parts of the body).

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 counselling and testing without waiting to develop symptoms and fall sick.

The incremental costs due to an additional one to two years on ART 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.

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). The introduction of targeted and/or routine viral load testing may reduce premature switching to costly second-line regimens.

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 in WHO's handbook for guideline development.

Summaries of the evidence for key recommendations reviewed by the guideline committee were produced by a range of academic institutions including Liverpool Medical School (UK), University of California, San Francisco (Cochrane Collaboration Center for HIV) (USA), University of New South Wales (Australia) and University of Bern (Switzerland), and in collaboration with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the Centers for Disease Control (CDC).

Consultations were also held with civil society networks including the Global Network of People living with HIV (GNP+), the International Treatment Preparedness Coalition (ITCP) and the International Community of Women with HIV/AIDS (ICW). These consultations explored the values and acceptability of WHO recommendations and identified and prioritized outcomes of importance to people living with HIV.

WHO is working with UNAIDS, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and PEPFAR on costing various treatment options. Appraisals are being conducted in low-income, high-burden countries to assess the feasibility of the recommendations.

The draft recommendations were subject to peer review from stakeholders and experts from around the world, including civil society representatives.

A multidisciplinary panel of experts in the ART guideline development group met 14–16 October 2009 to review, finalize and endorse the findings and recommendations, consider the balance of evidence for benefits and harms of these recommendations, and identify any uncertainties around the evidence, as well as the values, acceptability and implications of these recommendations. It also identified simple implementation tools required and key recommendations for future research.

DISSEMINATION AND IMPLEMENTATION

The key recommendations will be published on 30 November 2009 and the full guidelines are expected in early 2010. The release of the guidelines will be accompanied by regional consultations to introduce the revised recommendations to countries.

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.