

Technical Guidance Note for Global Fund HIV Proposals



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Treatment – antiretroviral therapy – infants, children and adults

This technical brief provides key technical information to guide proposal development and ensure that proposals include antiretroviral therapy in comprehensive HIV care and treatment services. The prevention and assessment of HIV drug resistance and pharmacovigilance are covered in more detail in separate technical guidance notes.

Rationale for including this activity in the proposal

Antiretroviral therapy is important to reduce mortality, morbidity, HIV transmission and the number of children made vulnerable by HIV. Antiretroviral therapy should also link to other relevant national goals or targets, such as universal access goals and the Millennium Development Goals. The proposal may be used to optimize and augment existing programme activities outlined in the national HIV strategy; or add new programme activities, such as the prevention and assessment of HIV drug resistance, implementation of pharmacovigilance programmes, or expansion of access to first, second and third-line antiretroviral therapies. Infants, children and pregnant women are currently underrepresented in many treatment programmes and, in some countries, proposals may need to focus on other groups such as tuberculosis (TB) patients or people who inject drugs. To maintain treatment effectiveness, standardized simplified national guidelines for antiretroviral therapy are recommended for use in public and private sector (profit-making and non-profit-making) and activities to support prevention and assessment of HIV drug resistance at the population level are recommended. Pharmacovigilance activities are also important to monitor and capture short and long-term adverse events and toxicities related to antiretroviral drugs and other drugs used in HIV treatment, and use this information to improve programme outcomes.

In June 2010, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) launched Treatment 2.0, an initiative designed to achieve and sustain universal access and maximize the preventive benefits of antiretroviral therapy. Treatment 2.0 builds on the success of the previous "3 by 5" initiative, and uses programmatic and clinical evidence – as well as the experience over the last decade – to expand access to HIV diagnosis, treatment and care through innovations in five priority work areas:

1. Optimize drug regimens.
2. Provide access to point-of-care and other simplified diagnostic and monitoring tools.
3. Reduce costs.
4. Adapt delivery systems.
5. Mobilize communities.

The principles and priorities of Treatment 2.0 address the need for innovation and efficiency gains in HIV programmes to improve programme coverage, effectiveness and impact for both HIV-specific and broader health outcomes. To implement this initiative, WHO and UNAIDS are working with global partners, technical experts and other United Nations co-sponsors to establish short, medium and long-term targets and milestones. (See *The Treatment 2.0 framework for action: catalysing the next phase of treatment, care and support*, <http://www.who.int/hiv/pub/arv/treatment/en/index.html>.)

Elements to be considered in the situation analysis

Issues to consider include the:

- ◆ number of adults and children living with HIV, with breakdown on the proportion of adults who are pregnant women and the proportion of children who are infants, where this information is available;
- ◆ number of HIV-related deaths in a year;

- ◆ number of adults and children eligible for antiretroviral therapy;
- ◆ coverage of antiretroviral therapy services (disaggregated by sex, age, pregnancy status, other vulnerabilities and geography, including urban and rural distribution);
- ◆ number and level of health facilities providing antiretroviral therapy and HIV care, and the extent to which services are integrated and linked.

Examples of programme objectives

Common programme objectives for antiretroviral therapy are:

- ◆ to increase coverage of antiretroviral therapy for the adults and children living with HIV who need it from X% to Y%;
- ◆ to increase access to second-line antiretroviral therapy for X population;
- ◆ to increase access to antiretroviral therapy for infants and children, pregnant women or other groups living with HIV;
- ◆ to increase access of pregnant women to antiretroviral therapy and prevent mother-to-child transmission;
- ◆ to promote active surveillance for adverse events and toxicities related to antiretroviral drugs;
- ◆ to develop and implement a national strategy for HIV drug resistance prevention and assessment.

Focus populations

Focus populations for antiretroviral therapy are:

- ◆ adults and children currently on antiretroviral therapy (continue treatment);
- ◆ adults and children diagnosed with HIV and known to be eligible for treatment initiation, but not receiving antiretroviral therapy;
- ◆ adults and children diagnosed with HIV but not yet referred to or attending HIV care.

National guidelines should explicitly state the eligibility criteria; specify the standard regimens and options for specific target groups, such as patients with active tuberculosis or chronic hepatitis B; and be supported by a limited national formulary for both adults and children with a strong preference for fixed-dose combination formulations.

The number of people who are eligible for antiretroviral therapy can be estimated using the Spectrum HPP statistical software package, taking into account HIV prevalence, HIV-related mortality and the national population. In providing antiretroviral therapy, special attention needs to be paid to infants, children, pregnant women, people who are coinfecting with TB, people who inject drugs, and other specific or hard-to-reach groups identified locally.

Suggested activities

1. Review, update and adapt guidelines if necessary

- ◆ Treatment guidelines need to be reviewed from time to time in the light of new evidence and programmatic experience, and to ensure consistency with WHO's current treatment guidelines. Antiretroviral therapy guidelines for **adults and adolescents** were updated in 2010. WHO now recommends an earlier start to treatment for all HIV-positive individuals with a CD4-cell count of 350 cells/mm³ or less; and individuals with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4), active tuberculosis or active chronic hepatitis B, irrespective of CD4-cell count. The new recommendations are based on evidence of individual and public health benefits if treatment is started earlier. Countries are also urged to move away

from the least costly but more toxic regimens containing stavudine to regimens that contain zidovudine or tenofovir for all patients starting lifelong therapy. The recommendations also emphasize the importance of early HIV diagnosis and use of fixed-dose combination therapy, and outline an expanded role for laboratory monitoring of both CD4 and viral load to improve the quality of HIV treatment and care. Availability of these laboratory tests is not an absolute prerequisite for treatment, but it is desirable to ensure the greatest access to antiretroviral therapy. (See *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach*, 2010 revision (<http://www.who.int/hiv/pub/arv/adult2010/en/index.html>).

- ◆ Treatment recommendations for HIV-positive **infants and children** were also updated in 2010. It is now recommended that all infants and children less than 2 years of age with confirmed HIV infection should immediately start antiretroviral therapy, irrespective of CD4-cell count or clinical stage. In generalized epidemics, it is recommended that all infants have their HIV exposure status established as early as possible after birth. All known HIV-exposed infants need virological testing at or around 4–6 weeks of age to make an early diagnosis of HIV infection. Infants with HIV who have not received nevirapine as prophylaxis at birth, or whose mothers were not given nevirapine-based treatment or prophylaxis should start on a standard nevirapine-based first-line regimen. Infants with HIV who have received nevirapine as prophylaxis should start antiretroviral therapy with a lopinavir/ritonavir-containing treatment regimen. The new HIV paediatric recommendations can be found at <http://www.who.int/hiv/pub/paediatric/infants2010/en/>.
- ◆ **Nutritional support** for people living with HIV and their families may be required. People living with HIV have higher energy needs (10% higher for asymptomatic adults, 20–30% higher for symptomatic adults, 50–100% higher for children with weight loss) but reduced access to food due to morbidity, low productivity and poverty. Malnutrition and low body mass index increase the risk of early mortality after initiation of antiretroviral therapy by 2–6 times, irrespective of CD4-cell count. Food and nutrition programmes, as part of comprehensive care and support including antiretroviral therapy, are enablers of HIV treatment success. Nutritional support reduces early mortality after initiation of antiretroviral therapy and facilitates earlier recovery and return to productive, quality life within the family and community. Enrolment in a food and nutrition programme improves treatment adherence and reduces loss to follow-up. Food and nutritional support is limited to a period of 3–6 months, with clearly defined entry and exit criteria following nutritional recovery on antiretroviral therapy. Nutrition is particularly important for HIV-positive children, as significant programmatic experience and research evidence regarding HIV and infant feeding has shown. For more details see *Guidelines on HIV and infant feeding* (http://www.who.int/child_adolescent_health/documents/9789241599535/en/) and the SDA on nutrition.
- ◆ HIV-positive **pregnant women** need antiretroviral therapy if they are eligible, or combination regimens for prevention of mother-to-child transmission as outlined in the WHO antiretroviral therapy guidelines for adults and adolescents and the prevention of mother-to-child transmission guidelines, updated in 2010. For HIV-positive pregnant women, the new recommendations emphasize the crucial role of CD4 testing to identify those who need antiretroviral therapy and are at greatest risk of transmission, and advocate earlier and more efficacious antiretroviral prophylaxis options, including triple antiretroviral therapy. For HIV-positive women who are intending to breastfeed, antiretroviral prophylaxis for the mother or the infant should be provided throughout the breastfeeding period. See *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: recommendations for a public health approach*, 2010 version (<http://www.who.int/hiv/pub/mtct/antiretroviral2010/en/index.html>).
- ◆ According the 2010 WHO guidelines on antiretroviral therapy for adults and adolescents, all HIV-positive individuals with active TB should start antiretroviral therapy irrespective of their CD4-cell count and as soon as possible after initiation of TB treatment. Co-treatment for HIV and TB frequently requires modification of antiretroviral therapy regimens; usually the preferred NNRTI is efavirenz. Rifampicin has significant drug interactions with protease inhibitors and all protease inhibitors in standard doses are contraindicated. However, lopinavir and saquinavir may be used with an adjusted superboosted dose of ritonavir or double the daily standard dose of lopinavir. Alternatively, replacement of rifampicin for rifabutin can be considered with maintenance of PI drugs at standard doses.

- ◆ Hepatitis B and C are common among **people who inject drugs**. Patients with HIV and hepatitis B virus coinfection that need concomitant therapy should use an antiretroviral therapy regimen containing TDF and 3TC or TDF and FTC, as 3TC, FTC and TDF all have anti-HIV and anti-hepatitis B virus activity.
- ◆ WHO has recently released an adaptation guide as a resource for **policy-makers who are in the process of adapting or implementing national guidelines**. This advocates for a more integrated approach to adapting recommendations across all the guidelines, as these often overlap and intersect. Although the recommendations are in separate documents (adults and adolescents, paediatrics, HIV and TB, infant feeding and prevention of mother-to-child transmission), they need to be implemented together in a single health system. The adaptation guide contains guidance on the generic process of adaptation, and the specific challenges to adaptation and implementation posed by the new guidelines; and includes a series of illustrative case studies to showcase country examples of innovative approaches to adaptation. The document is available at http://www.who.int/hiv/pub/who_normative/en/index.html

2. Build human capacity through training

A key tenet of the WHO public health approach to antiretroviral therapy and HIV care is to increase capacity to deliver antiretroviral therapy through integrated and decentralized service delivery. The **Integrated Management of Adolescent and Adult Illness (IMAI)** and **Integrated Management of Childhood Illness (IMCI)** are the tools proposed by WHO to expand clinical service for adults and children at lower levels of the health-care system in resource-limited settings. IMAI and IMCI integrate simplified HIV clinical management into the routine work of existing health services with strong community linkages, with back-up from clinical mentors and referral to hospital. The tools cover the range of HIV-related prevention, care and treatment programmes, and support a district network model where health centres and district hospitals receive supportive supervision from clinical mentors within a strengthened consultative/referral and back-referral system.

IMAI and IMCI strengthen services at the level of communities, health centres and hospitals, and are implemented using a sequence of steps: introduction and orientation; country adaptation of IMAI materials; courses for district managers; training of trainers; sustained training support and supervision; emergency introduction to pre-service health worker training programmes, etc. Additional tools and support are available at <http://www.who.int/hiv/capacity/en/index.html>

3. Improve access to drugs and diagnostics

Access to HIV drugs and diagnostics is supported by WHO and many partners in the AIDS Medicines and Diagnostics Services (AMDS). Essential information is made available through the Global Price Reporting Mechanism, which lists and benchmarks prices for antiretrovirals, HIV diagnostics, TB drugs and malaria drugs. It also provides access to procurement information for opioid substitution therapy and oral morphine, and links to quality information about the drugs concerned (the WHO prequalification programme and US FDA tentative approval process). Logistics and supply management are supported by the partner organizations in the network, which can be contacted via the AMDS web site. For more information, see <http://www.who.int/hiv/amds/en/>

4. Strengthen patient retention and adherence

Adherence to antiretroviral therapy is an essential component of individual and programmatic treatment success. Programmes may seek to use Global Fund proposals to build in activities to promote and support patient retention and adherence. Programme elements that may be required include:

- ◆ fixed-dose combinations as preferred options in drug formularies;
- ◆ adherence counselling;
- ◆ subsidy or removal of user fees;
- ◆ development of people living with HIV as expert patients and community treatment supporters;

- ◆ adherence support tools for patient groups (children, caregivers, adults), such as diaries, pillboxes or reminder systems;
- ◆ pharmacy refill measures (pick-up pharmacy registers or dispensing records for antiretroviral drugs);
- ◆ modified strategies for directly observed therapy or supported therapy for specific groups such as prisoners, people who inject drugs, infants and pregnant women.

WHO can provide tools and protocols such as IMAI and IMCI to help strengthen adherence and retention.

5. HIV drug resistance prevention and assessment

Emergence of at least some level of HIV drug resistance is inevitable, given the virus's high replication and mutation rates, and the use of antiretroviral regimens that may not fully suppress the virus. Recent surveys have shown limited increases in the prevalence of HIV drug resistance. Concerns about resistance should not be an argument against the continued expansion of antiretroviral therapy coverage; however, it is important to ensure that the incidence of HIV drug resistance is minimized, and monitor its occurrence at the population level.

WHO, in consultation with WHO HIVResNet, recommends that countries develop a national strategy for prevention and assessment of HIV drug resistance. Preventing the rise of HIV drug resistance requires that antiretroviral therapy regimens are prescribed according to international treatment guidelines, and that patients are retained in care, adhere to antiretroviral therapy and have a continuous supply of quality-assured drugs. Specific protocols on how to monitor HIV drug resistance at the population level are available from WHO, along with technical assistance to develop national strategies for HIV drug resistance prevention and assessment. See <http://www.who.int/hiv/drugresistance/en/index.html> as well as the technical guidance note on HIV drug resistance for further information on how to include HIV drug resistance strategies in national plans and funding proposals.

6. Strengthen pharmacovigilance systems

The effectiveness of treatment programmes, particularly in low and middle-income countries, risks being compromised by problems related to toxicity, intolerance and drug–drug interactions. These adverse events – whether they are acute or chronic; mild or serious – are relatively common incidents affecting both individual patients and public health, but are only intermittently identified and rarely reported in low and middle-income settings. In strengthening pharmacovigilance (for antiretroviral drugs countries should consider:

- ◆ conducting a situation assessment, including mapping existing activities related to pharmacovigilance for antiretroviral drugs and evaluating needs;
- ◆ developing or reviewing national plans – where there is no pre-established pharmacovigilance system in the country, consider establishing a small number of sentinel sites;
- ◆ training health workers in pharmacovigilance;
- ◆ developing or reviewing national guidelines on the adverse effects of antiretroviral drugs;
- ◆ establishing a national expert working group on pharmacovigilance;
- ◆ establishing linkages with the International Drug Monitoring Centre.

Approach to costing these activities

A number of tools for costing antiretroviral treatment are available, including:

- ◆ the WHO Workplanning and Budgeting Tool, which helps countries develop a costed workplan and budget for Global Fund proposals;
- ◆ the WHO HIV/AIDS Unit Cost Calculator, which helps countries calculate unit costs of various HIV/AIDS activities;

- ◆ the Resource Needs Model, developed by the Futures Institute, which estimates overall resource needs for most activities;
- ◆ the Activity-Based Costing (ABC) model, developed for the AIDS Strategic and Action Plan (mechanism, which helps countries cost operational plans);
- ◆ the Clinton Health Access Initiative (CHAI), which also has costing tools for paediatric HIV treatment.

Information about the cost of medicines and diagnostics supporting antiretroviral therapy can be found in the Global Price Reporting Mechanism online database, published by WHO on behalf of the partners in the AMDS (see <http://www.who.int/hiv/amds/gprm/en/index.html>). The average cost of treating a person with antiretroviral therapy has decreased over time as systems become more efficient. Grant applicants should be aware of these downward trends and provide strong justification for their costing, as this will be closely scrutinized in an environment where demand for HIV services is increasing but budgets are constrained.

For the purposes of developing a Global Fund proposal budget, WHO recommends using the Workplanning and Budgeting Tool, available at <http://www.who.int/hiv/pub/toolkits/GF-Resourcekit/en/index2.html>

Suggested key indicators

Existing indicators in national programmes should be used wherever possible, but specific modifications to ensure that services for children are tracked are recommended. The Inter Agency Task Team (IATT) for prevention of mother-to-child transmission has been working with all IATT partners to improve guidance on programme monitoring and include additional indicators that address children.¹

Specific indicators for HIV drug resistance and pharmacovigilance are described in other technical guidance notes.

Availability	Coverage	Outcome/Impact
Existence of updated national policies and guidelines in line with international standards	Percentage of adults and adolescents with advanced HIV infection receiving antiretroviral therapy	Percentage of adults and children with HIV still alive and known to be on treatment 12 months after initiation of ART
Percentage of health facilities that offer ART (i.e. prescribe and/or provide clinical follow-up)	Percentage of infants with HIV receiving ART	Percentage of individuals who are still on treatment and who are still prescribed a standard first-line regimen after 12 months from the initiation of treatment
	Percentage of children (under 15 years of age or as locally defined) with advanced HIV receiving ART	

Linkages with other activities or programmes

Delivery of antiretroviral therapy requires effective linkages with programmes or services for:

- ◆ TB, viral hepatitis, voluntary counselling and testing, and prevention of mother-to-child transmission;
- ◆ maternal and child health, IMCI, infant and young child feeding;
- ◆ immunization;
- ◆ nutrition;
- ◆ national reference laboratory;
- ◆ essential medicines;

¹ More information can be obtained from WHO (Chika Hayashi, hayashic@who.int) or UNICEF (Priscilla Akpama, pakwara@unicef.org).

- ◆ community health programmes;
- ◆ pharmacovigilance.

Addressing gender, human rights and equity

Antiretroviral therapy needs to be made available and accessible to all people eligible, without discrimination. User fees for any portion of antiretroviral therapy services, including patient monitoring, adversely affect the uptake, adherence and success of programmes, particularly for poor and other vulnerable populations. Particular attention needs to be paid to reaching and sustaining treatment among:

- ◆ infants and children
- ◆ poorest and rural families
- ◆ adolescents and young mothers
- ◆ families who need HIV care
- ◆ people who inject drugs
- ◆ migrants and refugees
- ◆ prisoners.

Key implementing partners to consider

- ◆ Partners to consider include: Providers of antiretroviral therapy services, including public sector, nongovernmental organizations, FBO and private sector;
- ◆ National child and maternal health programmes;
- ◆ Actors in the national drug supply chain management system;
- ◆ Prevention of mother-to-child transmission programmes;
- ◆ US President's Emergency Plan for AIDS Relief (PEPFAR) implementers;
- ◆ Other development partners or United Nations partners (WHO, UNICEF, UNAIDS, UNFPA).

Type and sources of technical assistance for implementation

Technical assistance may be required for:

- ◆ strengthening drug procurement and supply chain management systems;
- ◆ improving laboratory services, including implementing mechanisms to allow for simplified diagnostics, including point-of-care technologies and dried blood spots;
- ◆ developing guidance on procurement activities for drugs, laboratories and other commodities, addressing good practice on storage, handling and disposal of materials and supplies;
- ◆ estimating and forecasting national requirements for antiretroviral therapy;
- ◆ developing or revising national policy and technical guidance documents, including dosing guidance for practitioners;
- ◆ developing phased implementation plans;
- ◆ developing programme activities to support monitoring and quality improvement;
- ◆ developing and implementing training, supervision and mentoring;
- ◆ HIV drug resistance prevention and assessment;
- ◆ pharmacovigilance.

