

WHO ANTIRETROVIRAL TREATMENT WORKING GROUP TREATMENT WHITE PAPER

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Audience: International and national policy makers, program planners, and those responsible for allocation of resources to HIV; donors, implementing partners, HIV clinicians and PLHIV.

Introduction

Significant progress has been made over the past five years in reducing the disparity in access to life-saving antiretroviral therapy (ART) for persons living with HIV (PLHIV) in resource-rich and resource-limited settings. Whereas only an estimated 50,000 people in sub-Saharan Africa had access to antiretroviral therapy in 2003, WHO/UNAIDS estimates nearly 3 million people in sub-Saharan Africa had access to ART by the end of 2008¹ with a nearly ten-fold increase in the number of people receiving antiretroviral drugs in low to middle income countries worldwide since 2003². These advances towards realizing the goal of universal access were made with substantial support of global health initiatives such as the Global Fund for AIDS, Tuberculosis and Malaria (GFATM), the US President's Emergency Plan for AIDS Relief (PEPFAR), UNITAID, the Bill and Melinda Gates Foundation and the Clinton HIV/AIDS Initiative building on country budgets and bilateral agreements. This increased access to ART has decreased HIV-related morbidity and mortality, and has improved the life-expectancy of individuals living with HIV worldwide^{3,4,5,6}. However, while the progress has been remarkable, there remains an enormous un-met need for treatment - and a need for a sustained and expanded response.

Growing Concerns over Sustainability

Despite recent reductions in HIV incidence, the number of people needing ART continues to grow, due to new infections and survival on ART. There is an expanding body of evidence reporting improved survival with the earlier initiation of antiretroviral therapy^{7,8}. Earlier initiation has also been linked to lower rates of HIV-related morbidity and mortality, as well as to reductions in the development of chronic medical co-morbidities not traditionally associated with HIV^{9,10}. Furthermore, studies continue to support synergistic prevention benefits for ART^{11,12}, adding further impetus to expand access to ART across the globe. The cost effectiveness of ART is not questioned; however the incremental costs associated with these changes can be substantial. More expensive yet patient friendly ART regimens are increasingly used as preferred initial options due to fewer long-term side effects. In addition, improved access to antiretroviral therapy has increased demand for supportive laboratory techniques such as CD4+ cell and viral load monitoring.

These changes in clinical strategies have the potential to dramatically increase upfront programme costs for treatment, while the ongoing global economic crisis threatens sustained financial investment nationally and internationally. With all this in mind, the upcoming 2009 revision of the *World Health Organization Guidelines for Antiretroviral Therapy for HIV Infection in Adults and Adolescents* will attempt to incorporate the best available evidence under a framework that emphasizes the public health approach to maximizing enrollment into quality HIV care and treatment.

It is also critical that as National ART Programme and public health leaders consider changes in their national HIV treatment recommendations, they do so in the context of a rational public health approach rooted strongly in knowledge of the national HIV epidemic, the strengths and weaknesses of the health system, relevant legal policies, and the availability of fiscal and other resources within the country. Simultaneous adoption of multiple new clinical strategies meant to improve clinical care has the potential to precipitously increase programme costs and lead to adverse consequences, particularly in countries with high burdens of HIV infection. In 2008, the adoption of more costly first line regimens in several countries placed in significant jeopardy the ability of those countries to guarantee delivery of ART to all those clinically eligible. Indeed, many countries are still struggling to ensure ART to people in immediate need.

Updating national treatment recommendations therefore requires assessments and strategic planning to avoid undermining treatment programmes, protect access for at-risk populations and ensure the sustainability of the treatment programmes themselves. Key cost effective interventions should be identified and prioritized according to country context. *It is of paramount importance that national and international policy makers, program planners, donors, development partners, and those ultimately responsible for allocation of resources to HIV support local decision-making processes to equitably and sensibly update recommendations with the intent of securing the greatest positive impact for the greatest number of people over the long term.* This white paper is intended to serve as a resource for country programmes to consider as they strive to make the best possible decisions for their programmes.

Principles for Revising National Treatment Guidelines

Countries should consider the following principles to guide decision-making about introducing revised ART guidelines:

1. **“First, Do No Harm”** – Seek to maintain the current progress of treatment programs without disrupting the care of those on treatment or compromising PLHIV at highest risk for poor outcomes.
2. **Access** – Ensure all eligible people with HIV are able to enter treatment services
3. **Quality** – Ensure that care achieves the highest standards possible within a public health approach.
4. **Equity** – Ensure fairness and justice in the distribution of treatment services.
5. **Efficiency** – Achieve the greatest health impact with the optimal use of available human and financial resources.
6. **Sustainability** – Understand the long-term consequences of changes with the vision of providing continued, life-long access to ART for those in need.
7. **Forward looking** - be mindful of the need to accelerate adoption of new evidence and new technologies into programming, and time to overcome delays to achieving implementation.

With resource limitations in the face of a growing need for ART, program planners will need to be particularly sensitive to inherent tradeoffs between these principles.

While these principles should be used to guide decision-making, it is not expected that all countries will come to the same decisions. There are important differences between countries - the available resources and capacity, current program performance, and in the values that society holds most important. It is important to engage stakeholders – including PLHIV, civil society and health care workers – in frank and honest discussions about how to prioritize changes to ART guidelines (e.g. increasing CD4 thresholds for initiation, changing preferred ART drugs in first line regimens, or introducing viral load testing to confirm treatment failure).

Practical Approaches to Move Forward

The following practical approaches may assist decision makers in optimizing care and treatment programmes:

1. **Assess the relative health impact of the HIV epidemic compared to other pressing health needs.** Is the additional investment in HIV justified given other health priorities? Is there tension between society's values, HIV-positive people's needs and competing public health priorities? Are prevention policies based on an accurate understanding of the local epidemic and is this information leveraged to maximize additional investments in HIV care and treatment? Is this understanding of the local epidemic also used for the advancement of other health-related millennium development goals (MDGs), including maternal and child health (MDGs 4&5)?
2. **Perform a risk-benefit assessment [Table 1].** Risk assessments need to take into consideration multiple factors which include the status of treatment scale-up and implementation, the number of people still in need of treatment, anticipated funding streams, and the ability of the health system to adapt to changes.
3. **Assess how anticipated guideline changes will impact the health system.** How will existing and additional resources synergize with other areas of the health sector, and further strengthen health systems? How can redundancies that create parallel infrastructure or decrease the efficiency of the health system be avoided? Plans for implementing changes in the guidelines will be most effective if specifically designed to strengthen existing health systems.

Table 1. Elements to include in Risk-Benefit Assessments of changes to ART Programmes	
Elements	Sample Scope
Current and projected levels of ART coverage	How successful have present efforts been at reaching those in need at current CD4 thresholds? Are there particular gaps that need to be addressed (e.g. access for pregnant women or children, IDUs, prison settings, MSM)? Are targets established?
Anticipated needs under new eligibility criteria	What is the scale of the likely increase in ART demand?
Effect on special populations (e.g. pregnant women, children, TB co-infected, IDUs, Hepatitis B & C, people living in closed settings such as prisons)	Would changes have any unintended effects on special populations? Conversely, could early prioritization of special populations help phase-in changes?

Current and projected laboratory capacity	Will the current number of routine and specialized laboratories be sufficient? Will changes require new technologies? How will changes impact lab budgets?
Policies and guidelines in place	Are there any critical policy obstacles to implementation, e.g.: policy on PITC; user fees?
Current and projected ART delivery site capacity	How will changes impact the physical and human resource needs of ART clinics? Will new infrastructure be required? What resources would be needed to help health care workers cope with increased work load?
Current and projected capacity of systems to forecast, procure, store, and deliver needed commodities	Would additional infrastructure or human resources be required?
Implications for training and retraining	Will the changes require additional training? Has there been an effort to minimize the disruption of training (pre and in service)?
Current and projected costs	What are the anticipated total costs resulting from possible changes in HIV treatment guidelines (including both HIV program costs and conservative estimates of potential cost-savings from decreased hospitalizations, etc)? Could changes to procurement patterns lead to cost increases or reductions (e.g. through economies of scale)?
Current and projected level of financial resources, including plans and opportunities for future funding within country and from outside donors	Can current or projected commitments meet any increased need due to guideline changes? What commitments can be made by stakeholders for the future? Are funding streams secure and is there a national strategy to secure additional sources of funding?
Acceptability of changes among key stakeholders (PLHIV, health care workers, civil society, parliamentarians)	Is there support for implementing changes from key stakeholders and those most directly involved with care? Has effort been dedicated to involving key stakeholders in the decision making process?
Sustainability of changes over time	What is likelihood that changes can be implemented and sustained over time?
Potential effects on health systems	Would changes help strengthen existing health systems or could they divert resources away from other existing programs? Particular attention should be paid to the six building blocks ¹³ of health systems. How planned activities integrate with plans for other health issues (e.g. TB, MCH, treatment of drug dependency, viral hepatitis etc.)?

Particular care should be taken to outline unintended consequences that might result from potential changes. For example, by increasing the number of people eligible for ART without ensuring commensurate resources could result in stock-outs or implicit rationing¹⁴; this could unintentionally limit access to ART and shift resources away from those in greatest immediate need of treatment¹⁵. However, it is important to *not* let limitations serve as an insurmountable barrier to implementing important changes to ART guidelines. Rather, after identifying potential risks posed by changes to ART programmes, a strategic plan outlining how to achieve a smooth transition to new recommendations should be developed [Figure 2]. A key element of planned transitions should include explicit steps to achieve cost efficiencies [Table 2].

Figure 2. Core Steps in the Development of a Strategic Plan to Implement Guideline Changes.

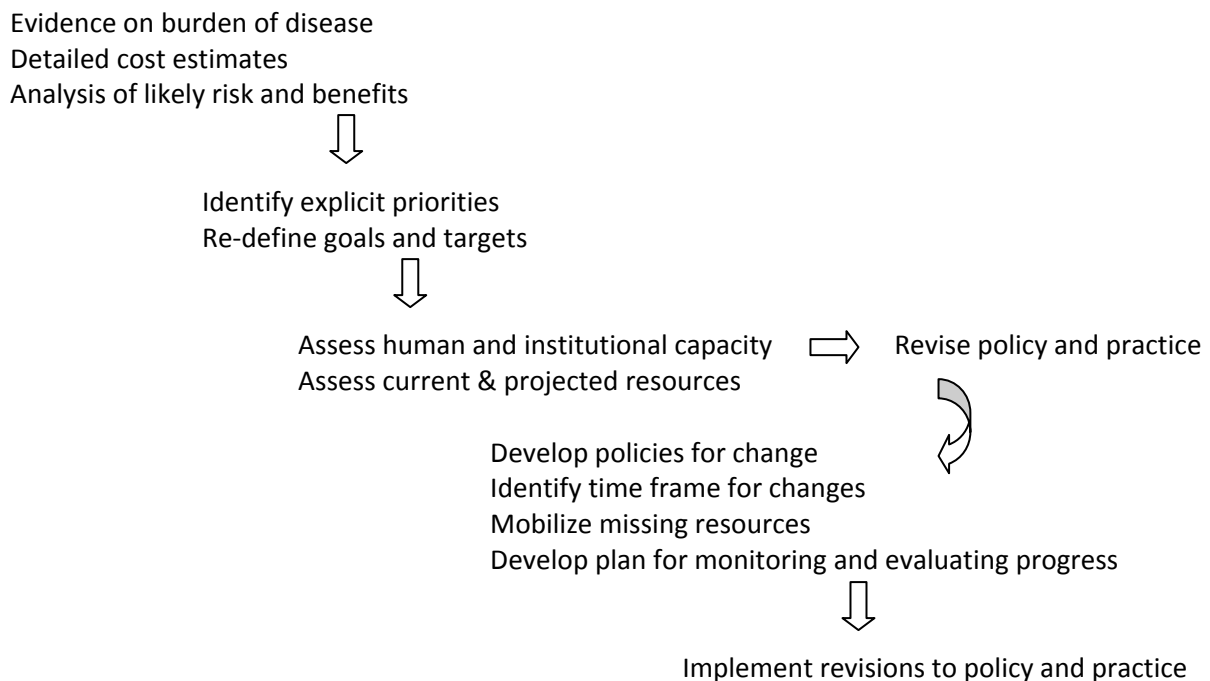


Table 2. Potential steps to achieve cost efficiencies in antiretroviral therapy programs	
Aim	Examples
Minimizing commodity cost	<ul style="list-style-type: none"> • Conduct accurate costing and forecasting • Ensure timely registration and approval of new formulations of ARVs • Use pooled procurement with other countries to minimize prices • Conduct regular reviews of ARV and reagent costs with preference for lowest-cost drugs (e.g. quality generic, fixed-dose combination) or lab reagents
Smooth transition to new recommendations	<ul style="list-style-type: none"> • Ensure optimal competence and stakeholder representation within national treatment working groups • Use a phased approach of prioritizing treatment at higher CD4 initiation thresholds for pregnant women, children, TB-HIV co-infected patients, IDUs, hepatitis B & C , marginalized or vulnerable populations until the system is able to accommodate changes for all patients • Use a phased approach of continuing lower-cost regimens for stable patients while beginning transition to new regimens with patients newly initiating HAART
Optimize models of health service delivery	<ul style="list-style-type: none"> • Examine efficiencies in the current service delivery model • Use task shifting and task sharing to most effectively utilize existing human resources; introduce new cadres of health workers if appropriate • Reduce frequency of health visits for stable patients • Decentralize services through integration with existing primary care services
Support health maintenance in populations before they need ART	<ul style="list-style-type: none"> • Optimize pre-ART care services (e.g. cotrimoxazole prophylaxis, INH prophylaxis ,selected vaccines, safe drinking water and hygiene services, nutritional, psychological and social support, needle syringe exchange and opiod substitution therapy)
Identify and address systems bottlenecks	<ul style="list-style-type: none"> • Meet regularly with service providers and recipients to gather feedback (including usability of guidelines, demand constraints), lessons learned and suggestions for improvement • Ensure effective data collection and analysis at all levels • Conduct regular supervision and program evaluations

The Importance of Moving Forward Responsibly

Given the cost constraints facing many nations in the fight against HIV, there is the very real possibility that incorporation of guideline changes without a strategic plan for implementation may reverse some of the dramatic gains realized earlier this decade. While the responsibility lies with national ART programmes to ensure that changes are introduced to the National guidelines in the most equitable and fair manner possible, it is equally important that the global community does not let the gap in HIV treatment between the north and south widen. There must be a *sustained* effort from all international partners and donors to support countries most affected by HIV to continue to respond to the growing need for HIV treatment.

Resources Available

The World Health Organization Global Treatment Working Group (GTrWG) is committed to achieving the goal of universal access to high quality ART services worldwide. While recognizing that this will not be an easy process - especially in times of economic uncertainty and other pressing commitments - the GTrWG will attempt to support countries in moving forward through a variety of means:

- Regional meetings to introduce guideline revisions, review potential impact and engage in strategic planning and target setting to implement changes;
- Linkages to foster cross-country learning and south-south collaboration;
- Advocacy to maintain and augment financial investment in HIV treatment;
- Providing technical assistance in the development of risk-benefit and feasibility assessments of guideline changes;
- Linking to technical assistance to assist with programme costing and scenario-based modeling to identify likely efficiencies and improve programme planning ;
- Dissemination and development of tools and technical assistance to support local adaptation and decision making;
- Linking to technical assistance and other support for implementation of an appropriate monitoring and evaluation process;
- Identification of other potential sources of support for countries .

Conclusion/Key Points

Adoption of elements of the planned revisions of *World Health Organization Guidelines for Antiretroviral Therapy for HIV Infection in Adults and Adolescents* will offer countries substantial potential health gains, but will likely raise upfront costs. Unfortunately, this comes amid the backdrop of budget constraints associated in part with the global recession, a persistent HIV epidemic, and significant health systems constraints to delivering universal access to ART treatment, especially for high burden countries. *Strategic country-level decision making will be critical to most equitably and sensibly update treatment recommendations with the goal of ensuring the greatest benefits on the greatest number of people.* While the current resource gap has the potential to reverse some of the progress in closing the gap in treatment coverage between resource-rich and resource-limited settings, it also provides us with the opportunity to improve the efficiency of how HIV care is delivered. This can help reduce overall costs and improve outcomes for patients and programmes. Furthermore, it is imperative that the global community sustain financial and technical support towards closing the treatment gap.

Addendum

The WHO Global Treatment Working Group is comprised of representatives from key international stakeholders, donors and implementers engaged in HIV care and treatment. The group provides a forum for in-depth scientific discussions and problem solving on emerging issues in ART provision and program implementation; and seeks to coordinate and harmonize efforts in order to multiplying the health impact of the individual organizations. The group currently has representation from the World Health Organization; UNAIDS; UNITAID; the PEPFAR Adult Treatment Technical Working Group; Global Fund for TB, AIDS, and Malaria; International AIDS Society; the Clinton HIV/AIDS Initiative, World Bank and TASO.

¹ Towards universal access: scaling up priority HIV/AIDS interventions in the health sector. Progress report, September 2009. Available at <http://www.who.int/hiv/pub/2009progressreport/en/>.

² Joint United Nations Program on HIV/AIDS. *2009 Report on the Global AIDS Epidemic*. UNAIDS. November 2009. http://data.unaids.org/pub/Report/2009/2009_epidemic_update_en.pdf.

³ Lowrance D, Makombe S, et al. A Public Health Approach to Rapid Scale-up of Antiretroviral Treatment in Malawi 2004-2006. *J Acquir Immune Defic Syndr*. November 2008, 49(3):287-293.

⁴ Lowrance D, Ndamage F, et al. Adult and Clinical Immunological Outcomes of the National Antiretroviral Treatment Program in Rwanda during 2004-2005. *JAIDS*. September 2009, 52(1): 49-55.

⁵ Bendavid E, Bhattacharya J. The President's Emergency Plan for AIDS Relief in Africa: An Evaluation of Outcomes. *Annals of Internal Medicine*. May 2009, 15(10): 688-695.

⁶ Adult mortality and antiretroviral treatment roll-out in rural KwaZulu-Natal, South Africa. Herbst AJ, Cooke GS, et al. *Bull World Health Organ*. 2009 Oct;87(10):754-62.

⁷ A Randomized Clinical Trial of Early Versus Standard Antiretroviral Therapy for HIV-Infected Patients with a CD4 T Cell Count of 200-350 Cells/ml (CIPRAHT001). Severe P, Pape J, Fitzgerald D et al. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy; San Francisco, 2009; Abstract H-1230c.

⁸ When to Start Consortium. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*, 2009, 373:1352-1363.

⁹ SMART Study Group. Risk for Opportunistic Disease and Death after Reinitiating Continuous Antiretroviral Therapy in Patients with HIV Previously Receiving Episodic Therapy. A Randomized Trial. *Annals of Internal Medicine*. September 2008, 149(5):289-99.

¹⁰ Weber R, et al. CROI 2005. Abstract 595.

¹¹ Gray R, et al. *Lancet*. 2001, 40:1149-1153.

¹² Castilla J, et al. *J Acquir Immune Defic Syndr*. 2005, 40:96-101.

¹³ World Health Organization. *Everybody's Business: Strengthening Health Systems to Improve Health Outcomes: WHO's Framework for Action*. WHO, 2007.

¹⁴ Bennett S, Chanfreau C. Approaches to rationing antiretroviral treatment: ethical and equity implications. *Bulletin of the World Health Organization*. 2005, 83(7): 541-547.

¹⁵ Improving Outcomes in State AIDS Drug Assistance Programs. *J Acquir Immune Defic Syndr* 2009;51:513-521).