



WORLD HEALTH ORGANIZATION'S 2010 RECOMMENDATIONS FOR HIV TREATMENT: NATIONAL GUIDELINE REVISION CHALLENGES AND LESSONS LEARNED

TECHNICAL BRIEF

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INTRODUCTION

In 2002, the World Health Organization (WHO) first published guidelines for a public health approach to scaling up antiretroviral therapy (ART) in resource-limited settings. These guidelines were simplified in 2003 and revised in 2006. Throughout 2009, WHO engaged with multiple stakeholders to update HIV treatment guidelines, culminating in the dissemination of *Rapid Advice: Antiretroviral Therapy for HIV Infection in Adults and Adolescents* in late November 2009 (WHO 2009b). Table 1 lists eight key *Rapid Advice* recommendations. The full revised guidelines, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach* (July 2010 version), expanded on *Rapid Advice* and were released in July 2010 (WHO 2010a).

The key messages that emerged from these recommendations were earlier initiation of ART, the use of

less toxic treatment regimens, and an expanded role for laboratory monitoring, including both CD4 testing and viral load (VL) monitoring (WHO 2010a).

Although the scientific evidence in support of these recommendations is compelling, national programs in resource-limited settings throughout the world are encountering challenges with their adoption and implementation. The aim of this technical brief is to provide policymakers and program managers with a point of reference as they adapt and implement revised national treatment guidelines.

Much of the information contained in this brief is derived from grey literature and key informant interviews. Approaches that worked well, challenges, and lessons learned from three regions of the world—sub-Saharan Africa (South Africa, Tanzania, Zambia, Zimbabwe), Latin America (Guyana, Honduras, and Nicaragua), and Southeast Asia (Cambodia)—are

	Key Recommendations
1.	Start antiretroviral therapy (ART) in all patients with HIV who have a CD4 count of less than 350 cells/mm ³ , irrespective of clinical symptoms.
2.	Start one of the following regimens in ART-naïve individuals eligible for treatment. <ul style="list-style-type: none"> • Zidovudine (AZT) + lamivudine (3TC) + efavirenz (EFV) • AZT + 3TC + nevirapine (NVP) • Tenofovir (TDF) + 3TC or emtricitabine (FTC) + EFV • TDF + 3TC or FTC + NVP
3.	Start ART in all individuals living with HIV with active tuberculosis, irrespective of CD4 cell count.
4.	Start ART in all individuals living with both HIV and hepatitis B virus who require treatment for their hepatitis B virus infection, irrespective of CD4 cell count or WHO clinical stage.
5.	Start ART in all pregnant women with HIV and a CD4 count of less than 350 cells/mm ³ , irrespective of clinical symptoms.
6.	Where available, use viral load (VL) to confirm treatment failure. <ul style="list-style-type: none"> • Where routinely available, use VL every six months to detect viral replication. • A persistent VL above 5,000 copies/mL confirms treatment failure. • When VL is not available, use immunological criteria to confirm clinical failure.
7.	A boosted protease inhibitor (bPI/r) plus two nucleoside analogues are recommended for second-line ART. <ul style="list-style-type: none"> • For second-line ART, atazanavir/ritonavir (ATV/r) and lopinavir/ritonavir (LPV/r) are preferred.
8.	National programs should develop policies for third-line therapy that consider funding, sustainability, and equitable access to ART.

Source: WHO 2009b

highlighted. Links to key resources for countries revising guidelines and implementing revisions are also provided.

PROGRAM CONSIDERATIONS

Sub-Saharan Africa is the region of the world most heavily affected by the HIV epidemic, accounting for over 67 percent of all people living with HIV (PLHIV). Adult HIV prevalence in the region is five percent, but the epidemic varies significantly from country to country. The nine countries of Southern Africa bear a disproportionate share of the global HIV burden, with each having an adult HIV prevalence greater than 10 percent. Heterosexual intercourse is the driving force for the epidemic in the region (Joint United Nations Programme on HIV/AIDS [UNAIDS] and WHO 2009).

Asia, home to 60 percent of the world’s population, is second only to sub-Saharan Africa in terms of the number of PLHIV. With the exception of Thailand, every country in Asia has an adult HIV prevalence of less than one percent. The regional adult HIV prevalence in South and Southeast Asia is 0.3 percent. Asia’s epidemic is largely concentrated in specific populations: sex workers and their clients, men who

have sex with men, and people who inject drugs. Latin America is primarily home to low-level and concentrated epidemics with a regional adult HIV prevalence of 0.5 percent. Men who have sex with men account for the largest share of HIV infections in Latin America, with epidemics also concentrated among sex workers and people who inject drugs (UNAIDS and WHO 2009).

In recent years, much progress has been made in scaling up access to HIV treatment worldwide, as the global health community continues to work toward universal access (defined as providing treatment to at least 80 percent of patients in need). Table 2 provides HIV data for three key regions of the developing world, including estimated ART coverage. In 2009, an estimated 3.91 million people were receiving ART in sub-Saharan Africa, a 33 percent increase from the previous year. East, South, and Southeast Asia increased ART patients by approximately 29 percent in 2009 to 739,000. Latin America had an approximately 6 percent increase from 2008 with 425,000 people receiving ART in 2009. However, much work remains to be done to increase ART coverage to the level of universal access from 2009 rates of 37 percent in sub-Saharan Africa; 31 percent in East, South, and Southeast Asia; and 51 percent in Latin America (WHO 2010b). Global data indicate that “achiev-

Region	Adult HIV Prevalence (2009)	People Receiving Antiretroviral Therapy (December 2009)	Estimated People in Need of Antiretroviral Therapy (December 2009; Based on WHO 2010 Guidelines)	Estimated Antiretroviral Therapy Coverage (December 2009; Based on WHO 2010 Guidelines)
Sub-Saharan Africa	5.2%	3,911,000	10,600,000	37%
East, South, and Southeast Asia	<0.2%	739,000	2,400,000	31%
Latin America	0.6%	425,000	840,000	51%

Sources: UNAIDS and WHO 2009; WHO 2010b

ing 80 percent treatment coverage by 2015 would require 49 percent more person-years of treatment with eligibility at <350 [cells/mm³] but would reduce AIDS deaths by 22 percent and reduce the number of new infections by 11 percent” (Stover, Bollinger, and Avila 2010).

A recent study in South Africa used mathematical modeling to predict resource requirements for full implementation of the new WHO treatment guidelines during the first five years. The study’s findings estimated that approximately seven percent extra annual investments would be required, but predicted a profound impact on HIV incidence leading to lower annual costs after seven years. The study concluded that the “resulting cumulative net costs reach a break-even point after on average 16 years,” and that “apart from the benefits associated with many life-years saved, a modest frontloading appears to lead to net savings within a limited time horizon” (Hontelez et al. 2010, abstract).

WHO has acknowledged that “immediate and full adoption of these recommendations may not be practical, feasible or affordable” (WHO 2009a, 4). However, WHO advises that “country planning should be directed towards the goal of their eventual implementation” (WHO 2009a, 4). A study was recently completed to provide data on the potential impact of prioritizing certain recommendations over others (Walensky et al. 2010a). When the new guideline recommendations were considered separately, they found that five-year survival would be maximized by initiating ART at $CD4 \leq 350$ cells/mm³ (87 percent survival) compared with adding second-line ART (66 percent) or substituting tenofovir (TDF) for stavudine (d4T; 66 percent). Therefore, implementation of ART initiation at a $CD4$ count of ≤ 350 cells/mm³ alone was found to provide the greatest short- and long-term survival advantage and to be highly cost-effective. Providing access to

second-line ART was shown to provide more clinical benefits (e.g., greater life expectancies) than access to TDF, but to be less economically efficient. Overall, the data suggest that an appropriate sequence is implementation of earlier ART first, then d4T substitution with an alternative nucleoside reverse transcriptase inhibitor (NRTI), followed by provision of second-line ART in settings where simultaneous implementation of these recommendations is not feasible (Walensky et al. 2010a, 2010b).

GUIDELINE REVISION

WHO recommends that countries work through a 12-step process for revision of their national treatment guidelines, as described in Table 3. As of December 2009, 45 countries globally had already incorporated the new WHO recommendations on eligibility criteria and regimen choice for adults and adolescents into their national treatment guidelines (WHO 2010b). Countries are advised to “explicitly consider risks, benefits, and cost of new recommendations, as well as local values, preferences, resource requirements and limitations” (WHO 2009a, 11). According to WHO, the following four operational principles should guide country decision making throughout the guideline revision process (WHO 2009a):

- 1. Strengthen health systems:** Consider interventions that will strengthen health systems.
- 2. Implement in phases:** It will not be possible to implement every recommendation in every setting, so a phased-in approach is recommended.
- 3. Understand the perspectives of PLHIV:** The toxicity of d4T is of concern to the majority of PLHIV, and its continuing use may undermine confidence in ART. If d4T needs to be included in ongoing regimens, strategies should be devised

to allow for switching to an alternative drug in cases of toxicity, with a plan to eventually discontinue using this drug.

4. Be forward looking: The WHO guidelines on ART in adults and adolescents will next be updated in 2012. Countries should strive to adopt new recommendations prior to this.

1.	Establish a guideline review group.
2.	Decide on the composition of the guideline review group.
3.	Establish clear terms of reference for the group.
4.	Manage conflicts of interest.
5.	Prepare supporting materials to guide review group's decision making. Circulate supporting materials and 2009 <i>Rapid Advice</i> /2010 WHO recommendations to review group prior to scheduling a review meeting.
6.	Explicitly consider risks, benefits, and cost of new recommendations, as well as local values, preferences, resource requirements, and limitations (e.g., evidence assessment).
7.	Draft final recommendations to be included in the new guidelines.
8.	Set up and coordinate external, independent peer review of the new recommendations.
9.	Finalize the new guidelines.
10.	Develop a detailed and budgeted plan for introduction of the new guidelines.
11.	Facilitate health ministry review and approval.
12.	Publish and disseminate the guidelines.

Source: WHO 2009a

SUCCESSFUL STRATEGIES FOR GUIDELINE REVISION

Guideline revision can be challenging. Several approaches helped to expedite and improve the revision process in Tanzania, South Africa, Honduras, and Zambia. These strategies include streamlining

the revision process, partial adoption of earlier ART initiation, ensuring strong government leadership of the process, and forecasting and resource mobilization.

Streamline the revision process: After a country begins reviewing its national treatment guidelines, much time can pass before officially approved, revised guidelines are ready to disseminate (e.g., steps 1 to 12 in Table 3). Tanzania has taken a streamlined approach to the guideline revision process by first completing a feasibility review and rapidly prioritizing specific recommendations over others (e.g., steps 1 to 7), and then quickly skipping to step 11 for Ministry of Health (MOH) approval of the recommendations to be adopted.

Working closely with partner organizations, including WHO, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) agencies (e.g., the Centers for Disease Control and Prevention and the U.S. Agency for International Development [USAID]), and the Clinton Health Access Initiative, Tanzania's National AIDS Control Programme (NACP) reviewed the risks, benefits, and costs of WHO's new recommendations and assessed the feasibility of their implementation in the local context. This group, led by NACP, agreed that it would not be economically feasible to implement all of the new WHO recommendations across all patient populations simultaneously in Tanzania. Based on its feasibility analysis, which included robust cost estimates for antiretrovirals (ARVs) and laboratory supplies required to implement the new WHO guidelines over one year and five years, the group made recommendations to MOH policymakers for priority adoption of certain WHO recommendations, while leaving others for a later phase of implementation. The NACP is currently awaiting feedback from MOH policymakers on their recommendations, before completing the more lengthy steps 8 to 10.

These steps are usually more time-intensive than the others, because the guideline review group must draft revised guidelines, develop a budgeted implementation plan, and allow time for peer review of the draft guidelines. Tanzania's goal with this approach is to foster government commitment for rapid dissemination and to ensure the guideline review group's time is well spent on steps 8 to 10 by first securing high-level approval of the final recommendations to be included in the revised guidelines.

Partial adoption of earlier ART initiation:

WHO's 2010 guidelines recommend initiation of ART in all patients with a CD4 count of ≤ 350 cells/mm³, irrespective of clinical symptoms. However,

many countries in sub-Saharan Africa have been struggling for years to fund their national HIV treatment programs under an initiation threshold of 200 cells/mm³. Table 4 provides a summary of changes to the WHO guidelines between 2006 and 2010 about when to start ART in various types of HIV patients.

Although the benefit of earlier initiation to patients has been proven and accepted, the reality of increased patient loads in the context of severe budgetary constraints presents challenges for countries trying to adopt this new recommendation. Studies suggest that increasing the treatment eligibility criteria from ≤ 200 to ≤ 250 cells/mm³ results in an

TABLE 4. SUMMARY OF CHANGES TO THE WORLD HEALTH ORGANIZATION'S RECOMMENDATIONS ON WHEN TO START ANTIRETROVIRAL THERAPY		
Target Population	WHO 2006 Antiretroviral Therapy Guidelines	WHO 2010 Antiretroviral Therapy Guidelines
HIV-positive asymptomatic, antiretroviral (ARV)-naïve individuals	CD4 ≤ 200 cells/mm ³	CD4 ≤ 350 cells/mm ³
HIV-positive symptomatic, ARV-naïve individuals	WHO clinical stage II or III and CD4 ≤ 200 cells/mm ³ or WHO clinical stage III if CD4 not available or WHO clinical stage IV irrespective of CD4 or Consider treatment for WHO clinical stage III or IV and CD4 200 to 350 cells/mm ³ (but initiate before drops below 200 cells/mm ³)	WHO clinical stage II if CD4 ≤ 350 cells/mm ³ or WHO clinical stage III or IV irrespective of CD4
HIV-positive pregnant, ARV-naïve women	WHO clinical stage I or II and CD4 ≤ 200 cells/mm ³ or WHO clinical stage III and CD4 ≤ 350 cells/mm ³ or WHO clinical stage IV, irrespective of CD4	CD4 ≤ 350 cells/mm ³ , irrespective of clinical symptoms or WHO clinical stage III or IV, irrespective of CD4
HIV/tuberculosis co-infection, ARV-naïve individuals	Presence of active tuberculosis and CD4 ≤ 350 cells/mm ³	Presence of active tuberculosis, irrespective of CD4
HIV/hepatitis B virus co-infection, ARV-naïve individuals	No specific recommendation	Presence of chronic active hepatitis B virus, irrespective of CD4

Source: WHO 2010a

18 percent increase in the need for ART, while an increase to ≤ 350 cells/mm³ results in a 53 percent increase in need globally. The results by country vary from increases in the need for ART from 12 percent to 22 percent for the switch to ≤ 250 cells/mm³, and 33 percent to 62 percent for the switch to ≤ 350 cells/mm³ (Stover, Bollinger, and Avila 2010). Some countries have opted for partial rather than full adoption of WHO's 2010 recommendations by initiating ART earlier in some but not all subpopulations of HIV patients.

For example, South Africa has an HIV prevalence of 17.8 percent and the largest HIV treatment program in the world (UNAIDS 2009a). The country went through a feasibility review process prior to revision of its national treatment guidelines and found that full implementation of WHO's recommendation to initiate ART in all patients with a CD4 count of ≤ 350 cells/mm³ was not economically possible. It instead adopted a strategy of initiating only pregnant women and patients co-infected with tuberculosis (TB) who are ≤ 350 cells/mm³, while all other HIV patients are initiated on ART only when their CD4 count falls below 200 cells/mm³ or they develop stage IV disease. The South African government considers this an intermediate step until additional resources become available.

Strong government leadership: Ensuring government leadership and commitment is key for a successful guideline revision process. Honduras and Zambia provide examples of strong government leadership to revise the national treatment guidelines.

Honduras was in the process of completing the 2009 revisions to its national treatment guidelines and developing a new national HIV strategy at the time that WHO's *Rapid Advice* and subsequent 2010 recommendations were released. The Ministry

of Health decided to take an approach to guideline revision that would allow for rapid implementation of WHO's new recommendations and simultaneous finalization of a new national HIV strategy. The National AIDS Programme moderated an active, multi-stakeholder process of assessing the feasibility of the new WHO recommendations in the Honduran context. It was an open process of dialogue that included key international partner organizations such as the Pan American Health Organization and WHO, civil society, and PLHIV. Consensus on each recommendation was reached where possible.

Building on advice gleaned from the feasibility review process, the government of Honduras issued an official notification in December 2010 calling for mandatory and immediate implementation of the new CD4 threshold (e.g., initiation of patients on ART when their CD4 count is ≤ 350 cells/mm³, rather than ≤ 200 cells/mm³). Clinical coordinators from each of the 34 ART sites countrywide were members of the ARV Therapy Working Group, which had been providing technical input to the National AIDS Programme for close to 10 years. Through this forum, the clinical coordinators were advised of the implementation procedures for the government mandate, and these instructions were funneled back to health care workers at each of the ART sites in Honduras. All of the remaining WHO recommendations have been subsequently adopted and are being implemented in a similar fashion, although dissemination of officially revised national treatment guidelines has not yet occurred.

Zambia has a significant HIV burden, with prevalence of 13.5 percent (UNAIDS 2009b). Significant HIV funding has flowed into the country over the last decade from various multilateral agencies, bilateral donors, nongovernmental organizations, and private foundations. However, building consensus among this wide array of stakeholders can be

challenging. In January 2010, the Zambian MOH called an initial meeting to compare the new WHO recommendations with the current national treatment guidelines. The PEPFAR team; the National AIDS Council and other relevant not-for-profit organizations (e.g., the Centre for Infectious Disease Research in Zambia; the Zambia HIV/AIDS Prevention, Care and Treatment Partnership; John Snow, Inc.; and the Japanese International Cooperation Agency); private companies such as Konkola Copper Mines; the University Teaching Hospital; the Zambian Defense Force; and other stakeholders were invited. Private practitioners were also invited but did not attend. At this initial meeting, the MOH led a transparent and inclusive process by which participants reviewed and discussed each of the revised WHO recommendations. Each recommendation was considered individually for its appropriateness, feasibility, and acceptability within the Zambian context. The Ministry of Health effectively built consensus among various stakeholders while at the same time clearly articulating its vision and guiding the revision group to develop guidelines that were consistent with their local priorities. By December 2010, Zambia had completed the revision process, and the MOH began dissemination of the updated guidelines in 2011.

Forecasting and resource mobilization: Estimates indicate that the standard zidovudine (AZT)-based regimen is 30 percent more expensive than the standard d4T-based regimen, while the standard TDF-based regimen is 66 percent more expensive than the d4T-based regimens (Médecins Sans Frontières 2011b). WHO explicitly advises countries to consider the “cost of new recommendations...resource requirements and limitations” in step 6 of Table 3. Zambia has completed robust cost forecasting and quantification and successfully mobilized additional resources to cover the increased up-front costs associated with adoption of WHO’s 2010 recommendations.

In Zambia, the MOH was concerned about the significantly increased costs expected to be incurred if the WHO recommendations were implemented, especially in view of an expected funding gap for the national treatment program in the next few years. The Ministry of Health held meetings with key stakeholders to discuss the cost implications, both human and financial, of the recommended guideline changes. The Supply Chain Management System project, funded by PEPFAR through USAID, which provides logistics and supply chain management support to the MOH, was asked to provide cost estimates of each guideline change. These estimates suggested that an additional 70,000 patients require treatment immediately. The total additional costs calculated were estimated to reach between U.S.\$800,000 and \$1,000,000 over the next five years, including the anticipated costs of additional drugs and laboratory testing.

The Ministry of Health forecasted that existing stocks would be sufficient to absorb the additional drug needs up to the end of 2010. However, beyond 2010 it was estimated that funding would fall short of the amount necessary to purchase additional stocks, as many budgets were being phased out or flat-lined in 2011. However, the MOH remained committed to implementing the new CD4 initiation threshold and decided to adopt this new recommendation. Using these cost projections, the government of Zambia attempted to mobilize resources through the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) grants and the national budgetary process. The government applied for a GFATM Round 10 grant to support increased ARV procurement according to its quantifications, and the application was recently approved with an overall grant budget of approximately U.S.\$260 million (GFATM 2011).

Table 5 provides a summary of the successful strategies described which various countries have utilized to manage challenges with guideline revision.

TABLE 5. SUMMARY OF SUCCESSFUL IN-COUNTRY STRATEGIES TO MANAGE CHALLENGES WITH GUIDELINE REVISION		
Country	Challenge	Successful Strategy
Tanzania	Slow guideline revision process leading to delayed implementation.	Foster government commitment for rapid dissemination and ensure efficient use of the guideline review group's time by first securing high-level approval of the final recommendations to be included in the revised guidelines.
South Africa	Increased patient loads from revised CD4 initiation threshold of ≤ 350 cells/mm ³ .	Initiate antiretroviral therapy in all pregnant women and patients co-infected with tuberculosis with CD4 ≤ 350 cells/mm ³ . All other HIV patients initiate antiretroviral therapy when CD4 ≤ 200 cells/mm ³ or stage IV disease develops.
Honduras	Concurrent development of a revised national HIV strategy and revised guidelines, leading to delayed implementation of new recommendations.	Issuance of a government mandate for antiretroviral therapy initiation in patients with CD4 ≤ 350 cells/mm ³ that was funneled back to health care workers through clinical coordinators from every antiretroviral therapy site, prior to official guideline revision.
Zambia	Building consensus among a large number of HIV stakeholders while simultaneously achieving the vision of the Ministry of Health.	Transparent and inclusive multi-stakeholder process of guideline revision with strong leadership from the Ministry of Health.
	Increased up-front costs associated with new recommendations.	Robust cost forecasting and quantification to support a successful Global Fund to Fight AIDS, Tuberculosis and Malaria Round 10 application for additional HIV funding.

GUIDELINE IMPLEMENTATION

Once countries have completed the guideline revision process as outlined in steps 1 to 12 in Table 3, they should then move into the implementation phase. WHO acknowledges that “immediate and full adoption of these recommendations may not be practical, feasible or affordable” in every setting and recommends a phased-in implementation approach for some countries (WHO 2009a, 4). Countries should follow a step-by-step, budgeted implementation plan that is based on the findings from a review of the scientific evidence for each recommendation and a robust situational assessment. WHO further recommends that the following points be considered implementation priorities (WHO 2009a):

- Ensuring access to the most in need (e.g., CD4 count ≤ 200 cells/mm³, stage III or IV disease, and pregnant women)

- Determining when to start ART
- Determining what ART regimen to start
- Reducing the use of d4T
- Treating all PLHIV who have active TB with ART
- Introducing better laboratory monitoring.

As of December 2009, 33 countries globally had already started implementing d4T phase-out plans according to WHO's 2010 recommendation (WHO 2010b). Many other countries have begun implementing the recommendation of ART initiation in all HIV patients with ≤ 350 cells/mm³. Most countries were already practicing early initiation of pregnant women on ART, irrespective of clinical symptoms, prior to release of WHO's 2010 recommendations. Successful implementation strategies for all of WHO's 2010 recommendations, related challenges, and lessons learned from various countries are discussed in the following sections.

SUCCESSFUL STRATEGIES FOR GUIDELINE IMPLEMENTATION

Zambia, Guyana, and South Africa provide examples of some successful approaches to addressing challenges presented by implementation of the 2010 WHO recommendations. These approaches include rolling out national training of trainers workshops, mentoring social workers to address patient concerns, and implementing various task-shifting strategies.

Train Health Workers

Roll-out of new treatment guidelines requires in-service training of current health workers to 1) deliver high-quality services according to national protocols and 2) manage patient concerns associated with changes in drug regimens and dosing. Following finalization of revised HIV treatment guidelines in Zambia at the end of 2010, the guideline revision committee developed an orientation package highlighting the changes made from previous guidelines. A one- to two-day training of trainers workshop was planned with partner organizations and the MOH, and is presently being rolled out. Each district has an identified trainer/mentor who will be trained to lead the training workshop in their district for health care workers. Mentors are primarily medical officers. All 72 districts in Zambia will be targeted. The relevant district health management teams will be responsible for inviting key clinicians from each site to be trained.

Training will be repeated in high-density areas where needed, but all districts will receive a minimum of one training session. National coverage for training on the new guidelines will take an estimated two to three months. The costs of this training will be split between the cooperating partners, the sites, and the MOH. A formal assessment of the implementation process is planned after six to eight months.

Guyana began using TDF-based first-line therapy in 2006. All new patients initiating ART began TDF/emtricitabine (FTC) in combination with a non-NRTI, specifically nevirapine (NVP) or efavirenz (EFV). Guidance for the management of existing patients on d4T-based therapy recommended an immediate switch to a TDF-based regimen in the absence of contraindications. However, some patients were concerned about moving from the simple dosing of one pill with the d4T-based fixed dose combinations to the more complicated dosing of two different pills in the new TDF-based regimens. The Ministry of Health addressed this challenge by focusing on the role of the social workers and lay counselors at the ART centers. Ministry of Health staff advised social workers and counselors to use more effective counseling to increase ART patients' understanding of the benefits of the new regimen and the reasoning behind the switch. Patients were told that the new drugs reduced their risk of treatment failure and adverse side effects and therefore increased the quality of care they received.

Task Shifting

WHO's recommendation for a higher CD4 initiation threshold results in increased patient loads for health facilities that are already understaffed. The Ministry of Health in Malawi completed a feasibility appraisal of the new WHO recommendations and found that the number of people eligible for ART under the new CD4 cutoff of ≤ 350 cells/mm³ would increase by 30 to 40 percent (230,000 to 355,500) and would require an additional 780 full-time-equivalent health workers by 2014 (Chirwa et al. 2009).

One potential solution is task shifting, a strategy that delegates specific tasks to less specialized health care workers to ease the workload on doctors and nurses and save patients' time. Various task-shifting strategies implemented in South Africa, Zambia, and Guyana successfully eased the increased human resource

burden resulting from expansion of their national ART programs.

Since 2010, South Africa has conducted in-service training of nurses to initiate ART, which had previously been the responsibility of doctors. A study examined the total cost and potential cost savings of the national ART program in South Africa from 2010 to 2017 as a result of various scenarios including task shifting and lower drug prices. It found that task shifting alone would decrease total cost by 10 to 11 percent (Meyer-Rath et al. 2010). Zambia has launched a program similar to South Africa's. The General Nursing Council offers a year-long nurse practitioner course that qualifies nurses to prescribe ARVs and manage stable patients. It has also trained over 1,000 lay counselors to help with filling, adherence counseling, and patient flow. At several pilot sites, lay counselors have been trained to perform vital sign assessments, including height, weight, blood pressure readings, and temperature charting. Guyana has also successfully trained lay counselors to provide HIV counseling in the larger clinics and thus alleviate the bottleneck presented by long lines of patients waiting for counseling sessions with nurses. Table 6 provides

a summary of the successful strategies described that various countries have utilized to manage challenges with guideline implementation.

IMPLEMENTATION CHALLENGES

Countries are experiencing various implementation challenges associated with WHO's 2010 recommendations. Some of the key implementation challenges include supply chain management, d4T withdrawal, laboratory capacity, treatment for patients with TB, and second- and third-line therapy.

Supply Chain Management

WHO's 2010 recommendations have significant implications for the supply chain, and successful implementation of the recommendations requires that countries have strong supply chain management systems in place. National governments must effectively plan for procurement, storage, and distribution of all HIV commodities.

Country	Challenge	Successful Strategy
Zambia	Need for in-service training of health care workers nationwide on revised treatment guidelines.	Rapid, national roll-out of one- to two-day training of trainers workshops for health care workers using district trainers/mentors over a two- to three-month period.
	Shortage of human resources at antiretroviral therapy (ART) sites.	Preservice training of nurse practitioners to initiate ART; introduction of lay counselors to assist with administrative duties, patient counseling, and vital sign assessments at ART sites.
Guyana	Patient concerns with tenofovir (TDF) substitution and associated changes in drug dosing.	Mentoring of social workers at ART sites to deliver more effective patient counseling around the drug switch.
	Shortage of human resources at ART sites.	Introduction of lay counselors to assist with patient counseling at ART sites.
South Africa	Shortage of human resources at ART sites.	In-service training of nurses to initiate ART.

Planning with suppliers for increased ARV production: On April 1, 2010, South Africa officially began implementation of new national HIV treatment guidelines and simultaneously launched a massive national scale-up campaign for HIV testing and treatment, with a target of testing 15 million people in the first year. However, the revised treatment guidelines were disseminated only a few weeks prior to the April first implementation date. ARV suppliers did not receive any definitive notice or guidance from the government on the expected surge in ARV needs resulting from the new guidelines and national testing campaign. These suppliers could not ramp up ARV production quickly enough to meet the national program's implementation demands.

As a result of this limited ARV production, TDF for adult treatment was not available on the shelves at facilities until June/July 2010. Abacavir (ABC) solution for pediatric treatment and NVP suspension for the prevention of mother-to-child transmission program were not available until August/September 2010. Despite dissemination of the new guidelines and advance training of health care workers, the new guidelines could not be fully implemented, and patients could not get the newly recommended ARV drugs until several months after the government-mandated implementation date due to this lack of advance planning with suppliers.

Ensuring adequate stocks of laboratory reagents: In 2009, the MOH in Nicaragua updated the national ART guidelines; this included changing the CD4 cell count threshold to ≤ 350 cells/mm³ as an indication to start treatment regardless of VL. (Exceptions are made for patients with a CD4 count > 350 cells/mm³ if they have a VL $> 100,000$ copies/mL—they are also initiated on ART.) Surprisingly, the national HIV program did not experience a sudden increase in the number of patients eligible for ART. Following further investigation, it was determined that stockouts of

CD4 reagents occurred in early 2010. Despite revision to the national guidelines, the change in initiation criteria was not actually being implemented at the site level due to the unavailability of CD4 testing. Patients were only being initiated on treatment based on clinical symptoms alone.

Once the MOH resolved the issue of stocked-out CD4 reagents, another laboratory supply chain challenge arose. Problems with the new VL testing equipment that had been procured at the reference laboratory resulted in the unavailability of VL tests. Therefore, the expected surge in the number of patients eligible for ART when CD4 initiation criteria changed in 2009 was mitigated by a break in both CD4 and VL testing capacity due to supply chain problems. Now that these supply chain issues have been resolved and CD4 and VL testing is available in Nicaragua, the impact of the new CD4 initiation criteria on ART patient loads can be accurately assessed throughout 2011.

Overstock of old ARVs: When the 2006 revised guidelines were formally endorsed and disseminated to health facilities in Guyana, the MOH had a national overstock of ARVs for the old, d4T-based first-line therapy. They were not comfortable allowing all the old ARVs to expire unused, so they delayed distribution of the ARVs for the new TDF/FTC-based first-line therapy until more of the old ARVs had been consumed. This resulted in some confusion among health care workers who had been trained to use the new guidelines because the corresponding ARVs were not available to them at the health facilities. To address this challenge, ongoing updates were provided to the clinicians at the treatment sites about stock-on-hand of the old ARVs and orders for new ARVs.

Stavudine (d4T) Withdrawal

WHO recommends phasing out d4T and replacing it with AZT or TDF. Table 7 provides a summary of

changes to the WHO guidelines between 2006 and 2010 about which ARVs to start in various types of HIV patients. As of 2009 in low- and middle-income countries (excluding countries in the Americas), 59.7 percent of first-line ART patients were on d4T-based regimens, 32.1 percent on AZT-based regimens, and 7.7 percent on TDF-based regimens (WHO 2010b). Increased up-front costs are a major challenge that countries face as they withdraw d4T and substitute it with more patient-friendly yet more expensive first-line drugs. With HIV funding levels already low, AIDS activists have expressed concern that if these new, more expensive regimens are adopted, many people may fail to access treatment in the long run. A feasibility appraisal completed in Malawi estimated the additional costs (leaving all other costs unchanged) for substitution of d4T with a TDF-based regimen to be U.S.\$100 million, and U.S.\$50 million with an AZT-based regimen for the period up to 2014 (Chirwa et al. 2009). When comparing the costs of TDF against AZT, the additional cost of monitoring and treat-

ing the side effects that accompany the use of these drugs should also be considered.

Increased up-front costs: Cambodia updated its national treatment guidelines in 2010 but found inclusion of AZT or TDF in the first-line treatment to be cost prohibitive and decided against adopting this recommendation. However, Zambia and Zimbabwe are confronting the reality of these increased up-front costs.

In 2007, Zambia switched to TDF-based first-line therapy. The Ministry of Health issued stringent guidelines on which patients to switch and how to do so, including information on possible concerns such as a switch not being indicated, poor adherence, treatment failure, renal dysfunction, and patient preference. If patients were stable, did not have side effects, and did not wish to change drugs, they were kept on d4T. This resulted in a relatively gradual switch overall, as approximately 40 percent of patients remained on the

TABLE 7. SUMMARY OF CHANGES TO THE WORLD HEALTH ORGANIZATION'S RECOMMENDATIONS ON WHICH ANTIRETROVIRALS TO START		
Target Population	WHO 2006 Antiretroviral Therapy Guidelines	WHO 2010 Antiretroviral Therapy Guidelines
HIV-positive, antiretroviral (ARV)-naïve adults and adolescents	Zidovudine (AZT) or tenofovir (TDF) + lamivudine (3TC) (or emtricitabine [FTC]) + efavirenz (EFV) or nevirapine (NVP)	No change.
HIV-positive, ARV-naïve pregnant women	AZT + 3TC + NVP	<ul style="list-style-type: none"> • AZT preferred but TDF acceptable. • EFV included as preferred non-nucleoside reverse transcriptase inhibitor (non-NRTI) option (but do not initiate EFV during first trimester). • Benefits of NVP outweigh risks where CD4 count is 250 to 350 cells/mm³.
HIV/tuberculosis co-infection	AZT or TDF + 3TC (or FTC) + EFV	No change.
HIV/hepatitis B virus co-infection	TDF + 3TC (or FTC) + EFV	Non-NRTI regimens that contain both TDF + 3TC (or FTC) are required.

Source: WHO 2010a

d4T-based first-line therapy for several years. However, the WHO 2010 guidelines recommended a more aggressive transition, with rapid weaning of patients off d4T. After the Supply Chain Management System project conducted a comprehensive cost analysis, it was agreed that the process of transition from d4T- to TDF-based regimens should occur over a period of four years (up to the start of 2015), based on the assumption that this would be the most appropriate time period over which to absorb the increased costs of the switch. To promote a smooth transition, health care workers and lay counselors received training on the guidelines for switching patient regimens and appropriate patient counseling. Targeted media messaging of patients and caregivers through printed literature and radio was also conducted.

In May 2010, Zimbabwe released updated treatment guidelines that replaced d4T-based regimens with TDF-based regimens as first-line therapy, and also suggested initiating ART in all HIV-positive adults with a CD4 count of ≤ 350 cells/mm³ and in all HIV-positive pregnant women and infants regardless of their CD4 count or clinical stage. However, funding constraints have resulted in nearly a one-year delay in implementation of these new guidelines so far. The Permanent Secretary at the Ministry of Health and Child Welfare (MOHCW) sent a circular to implementing partners explaining that implementation of the new guidelines would officially begin April 1, 2011. It explained that, due to resource constraints, the new guidelines would be phased in over a three-year period. Because there were still significant stocks of d4T, the MOHCW mandated that all new patients be initiated on d4T until stocks were finished, while existing patients already experiencing side effects would be moved to TDF-based first-line therapy. The Ministry of Health and Child Welfare further mandated that all HIV-positive pregnant women eligible for ART be immediately placed on the new TDF-based regimens (PlusNews 2011).

Zimbabwe already has a very high treatment gap: around 226,000 people receive ART through the public health system, while another 340,000 are eligible for ART but have failed to access it. Recent estimates indicate that, under the new guidelines for earlier ART initiation, the treatment gap will increase, with at least half a million people qualifying for treatment. Dr. Owen Mugurungi, National Coordinator of the MOHCW's AIDS and TB Unit, has admitted that the new drug regimen is expensive but said in the long-term it would turn out much cheaper: "We may be able to put many people on ARVs now using the cheaper regimens, but five years from now we will be losing a lot of money...treating people for side effects from stavudine-based regimens" (PlusNews 2011).

Health care workers operating outside the national guidelines: South Africa and Tanzania have experienced a challenge when health care workers—aware that TDF is a superior drug—switch patients who do not meet the national eligibility criteria. As of April 1, 2010, when implementation of the revised treatment guidelines officially began, all new patients in South Africa were initiated on a TDF-based regimen. Existing patients were kept on d4T if stable and were only switched to TDF if they experienced toxicities. However, contrary to the national treatment guidelines, health care workers started switching their existing patients onto TDF because they knew it was a superior drug. This behavior became so widespread that it began to diminish stocks of TDF. It was feared that TDF supplies might end up so diminished that patients would experience a lapse in treatment or health care workers would have to switch patients back to d4T. The Director General of Health addressed this concern by sending out an official communication from his office ordering health care workers to follow the treatment guidelines carefully by keeping stable patients on d4T and only initiating TDF in new patients.

In Tanzania, the 2005 national treatment guidelines included both d4T and AZT as part of first-line therapy.

In 2008, the government began implementing a strategy of gradually phasing out d4T over a three-year period. In 2009, guidelines were officially updated to recommend that all new patients get initiated on AZT as the preferred first-line therapy. Tanzania is currently in the process of revising its national treatment guidelines in response to WHO's 2010 recommendations, but has not yet adopted TDF as first-line treatment. However, similar to South Africa's experiences, physicians are informed of TDF's merits, and the national program is finding that consumption rates of TDF have increased from previous years.

Laboratory Capacity

Many resource-limited countries struggle with weak laboratory capacity, characterized by under-trained laboratory personnel, broken or inadequate equipment, and limited funding for laboratory reagents and supplies, which contributes to poor screening and monitoring of HIV patients. In this context, countries are encountering significant challenges as they move to implement WHO's 2010 recommendations on CD4 testing for ART eligibility, increased VL testing, and hepatitis B virus (HBV) and TB screening.

CD4 testing: WHO's 2010 guidelines recommend initiation of ART in all patients with a CD4 count of ≤ 350 cells/mm³, irrespective of clinical symptoms. Historically, many resource-limited settings, especially in sub-Saharan Africa, have been using an ART initiation threshold of 200 cells/mm³. Patients with a CD4 count of ≤ 200 cells/mm³ will usually present at a health facility with more advanced disease (i.e., stage III or IV) than patients with a higher CD4 count. Clinical staging can often determine treatment eligibility in patients with advanced disease, but CD4 testing must be available to effectively screen patients for ART eligibility at higher CD4 counts. Access to CD4 testing can be especially limited at lower levels of the health system, due to lack of CD4 testing equipment and a shortage of trained laboratory personnel. Blood samples can

be transported to higher-level facilities for automated CD4 testing, but sample transport systems are often slow. Referral to higher-level facilities for a CD4 count requires strong patient referral networks and introduces additional barriers for the patient, including transportation costs and lost time at work or school, which can result in high loss-to-follow-up rates.

Honduras adopted WHO's recommendation of initiating ART in all patients with a CD4 count of ≤ 350 cells/mm³ while simultaneously rolling out a new HIV strategy that promotes expansion of first-line ART services to the primary care level. However, Honduras is finding that access to flow cytometry for automated CD4 testing, especially at the primary care level and among pregnant women in antenatal clinics, is a major implementation challenge. Most primary care clinics are only able to conduct manual CD4 testing, while higher-level facilities in Honduras have laboratory facilities that offer automated CD4 testing. A weak patient referral system, poor patient tracking, and the cost of transport mean that patients referred to higher-level facilities often receive delayed care or are lost to follow-up.

Viral load testing: WHO recommends that VL testing be used as part of a targeted strategy to confirm treatment failure, but cautions that "any decision on implementing VL testing should not undermine improved access to better ARVs, which should take priority if resources are limited" (WHO 2009a, 17). Most countries, including Honduras, Cambodia, and Zambia, are encountering challenges associated with implementation of this recommendation.

Honduras has adopted WHO's recommendation to expand the use of VL testing for monitoring of treatment failure, but access to the test is limited. Only one laboratory in the country has the capacity to carry out VL testing. The system for transporting blood samples from ART sites to the central laboratory is very slow, with a turnaround time of four to eight months

for results. To address this challenge, the MOH is building the capacity of two additional sites to offer VL testing in the future.

Cambodia adopted the recommendation that a persistent VL above 5,000 copies/mL confirms treatment failure. The national HIV program has a target of making 10,000 VL tests available in 2012 and 30,000 tests available in subsequent years. It also has plans for each ART patient to receive an annual VL test after being on treatment for two years. However, the cost of VL testing remains a major challenge for Cambodia's limited financial resources.

Viral load testing is available on a limited basis to patients in a few areas in Zambia, as determined by a testing algorithm that detects patients presumed to be failing treatment. It costs about U.S.\$27 per sample and is covered almost exclusively by partner organizations. To avoid unnecessary testing and preserve limited resources, only patients who are obviously experiencing clinical or immunological failure receive VL testing. While the limitations of this algorithmic approach were recognized during the guideline revision process, it was decided that the national program should continue with this approach and address the issues of prohibitive cost and limited VL laboratory capacity again in one year.

Hepatitis B virus screening: Hepatitis B virus is the leading cause of chronic liver disease and liver-related death worldwide, with the majority of these cases occurring in areas of Africa and Asia where HBV prevalence is high. Many of the countries affected by HBV are also affected by a high HIV burden, leading to frequent HIV/HBV co-infection. The consequences of co-infection include "increased liver-related morbidity and mortality, increased HBV viral replication, immune reconstitution to HBV in the setting of ART, and hepatotoxicity from ARVs" (Hoffmann and Thio 2007, 402). Laboratory capacity to screen for HBV in HIV patients is especially important in regions with high

HBV endemicity (prevalence greater than eight percent) and expanding ART programs (Hoffmann and Thio 2007). However, most resource-limited settings are struggling with limited funding for procurement of HBV testing supplies and with weak laboratory capacity for routine HBV screening.

The Western Pacific Region comprises 37 countries, including Cambodia (WHO Regional Office for the Western Pacific 2005–2011). This region contains only 28 percent of the world population, yet it is home to over half of the global deaths caused by HBV (Clements et al. 2006). Although Cambodia has adopted almost all of WHO's 2010 recommendations, it decided against adopting the recommendation to treat all HIV/HBV co-infected patients with ART, due to the cost and limited availability of HBV serodiagnostic and virologic tests. However, Cambodia's revised national treatment guidelines do include guidance on the use of TDF/lamivudine (3TC) instead of d4T for treatment of HIV patients who are already known to have chronic HBV.

Although Zambia adopted this WHO recommendation in its revised guidelines, weak laboratory capacity, higher costs for procurement of HBV testing supplies, and increased ART patient loads are challenging implementation. There are limited data on HBV prevalence in PLHIV in Zambia, but crude data based on blood bank statistics suggest an estimate of an additional 10,000 HIV patients who may need treatment (Mphahlele et al. 2002). Historically, ART sites in Zambia have not routinely screened PLHIV for HBV, and the national program does not currently have the systems in place to conduct wide-scale HBV screening.

Treatment for Patients with Tuberculosis

Tuberculosis is a major cause of death for PLHIV, hence WHO's recommendation to initiate ART in all patients with active TB. Though many countries have adopted this recommendation, diagnosing active TB

in PLHIV remains a challenge. Smear-negative TB is common in co-infected patients, and limited laboratory facilities hinder diagnosis by culture. In addition, diagnosing extrapulmonary TB is complicated by lack of access to histopathology and advanced imaging in the developing world. As a result, fewer than half of TB cases in PLHIV are diagnosed before death (Domousa et al. 1995; Lucas et al. 1993; Mohar et al. 1992). A new molecular TB test (GeneXpert MTB/RIF) endorsed by WHO simultaneously detects *Mycobacterium tuberculosis* and tests for rifampin resistance, reducing the time required to diagnose drug-resistant TB from up to three months down to less than two hours. The test can also detect TB more easily among people co-infected with HIV, in whom diagnosing TB is challenging. Médecins Sans Frontières is rolling out this new test in 16 countries in 2011 (Evans 2011; Médecins Sans Frontières 2011a).

An additional decision point for countries about this recommendation is when to start ART in co-infected patients. Many concerns have been raised about treating HIV and TB concurrently. Drug-drug interactions, drug side effects, and adherence within the setting of high pill burden are challenging to manage. Paramount among these concerns is the development of immune reconstitution inflammatory syndrome (IRIS). However, two recent randomized trials have shown that starting ART within four weeks of beginning TB treatment decreased the risk of death for patients co-infected with HIV (Abdool Karim et al. 2010; Havlir et al. 2011). Zambia is initiating ART in all patients with active TB within two to four weeks after starting TB treatment. Similarly, Cambodia's revised guidelines call for ART initiation in active TB patients within two weeks of TB treatment.

Second-Line Therapy

The price of second-line therapy remains considerably higher than first-line therapy, which presents a

challenge for resource-limited settings, especially as their national treatment programs grow older. In 2009, the weighted median cost per person per year for first-line therapy was U.S.\$137 in low-income countries and U.S.\$141 in lower-middle-income countries, compared to U.S.\$853 and U.S.\$1,378 for second-line therapy (WHO 2010b). WHO's 2010 recommendations include lopinavir/ritonavir (LPV/r) and atazanavir/ritonavir (ATV/r) as the preferred boosted protease inhibitors (bPIs) in second-line therapy. Table 8 provides a summary of changes to the WHO guidelines between 2006 and 2010 regarding second-line therapy for various types of HIV patients. A generic heat-stable formulation of LPV/r is on the market already, and a generic heat-stable fixed dose combination of ATV/r packaged together with TDF/3TC is under development (WHO 2010a). Historically, LPV/r has been the predominant bPI available in resource-limited settings, with 92.7 percent of adult second-line patients using it in low- and middle-income countries outside of the Americas (WHO 2010b). However, some countries, including Zambia, are beginning to consider use of ATV/r because of its anticipated cost savings.

In Zambia, LPV/r has been the recommended second-line bPI since 2005. However, Zambia has recognized the potential clinical importance and cost savings of ATV/r, which has a ceiling price of U.S.\$355 per patient per year, with further price reductions expected in the future, compared to LPV/r, with a ceiling price of U.S.\$399 per year (Clinton Health Access Initiative 2011). A gradual transition from LPV/r to ATV/r is planned in Zambia as soon as the drug has been registered and becomes available locally. To avoid confusion among care providers, the new guidelines briefly mention ATV/r but do not yet recommend the combination as part of second-line therapy. Once available, guidelines will be updated so that ATV/r will be recommended as an alternative to LPV/r, and appropriate provider training will be scheduled.

TABLE 8. SUMMARY OF CHANGES TO THE WORLD HEALTH ORGANIZATION'S RECOMMENDATIONS ON SECOND-LINE THERAPY		
Target Population	WHO 2006 Antiretroviral Therapy Guidelines	WHO 2010 Antiretroviral Therapy Guidelines
HIV-positive adults and adolescents	Zidovudine (AZT) + didanosine (ddl) or Tenofovir (TDF) + abacavir (ABC) or ddl + lamivudine (3TC) or TDF + 3TC (± AZT) plus Atazanavir/ritonavir (ATV/r) or fosamprenavir/ritonavir (FPV/r) or indinavir/ritonavir (IDV/r) or Lopinavir/ritonavir (LPV/r) or saquinavir/ritonavir (SQV/r)	<i>If stavudine (d4T) or AZT used in first-line:</i> TDF + 3TC (or emtricitabine [FTC]) + ATV/r or LPV/r
		<i>If TDF used in first-line:</i> AZT + 3TC + ATV/r or LPV/r
HIV-positive pregnant women	ABC + ddl or TDF + ABC or ddl + 3TC or TDF + 3TC (± AZT) plus LPV/r or nelfinavir (NFV) or SQV/r	Same regimens recommended for adults and adolescents.
HIV/tuberculosis co-infection	ABC + ddl or TDF + ABC or ddl + 3TC or TDF + 3TC (± AZT) plus LPV/r or SQV/r with adjusted dose of ritonavir (RTV) (i.e., LPV/r 400 mg/400 mg twice a day or SQV/r 400 mg/400 mg twice a day)	<i>If rifabutin available:</i> Same regimens as recommended for adults and adolescents.
		<i>If rifabutin not available:</i> Same nucleoside reverse transcriptase inhibitor (NRTI) backbones recommended for adults and adolescents, plus LPV/r or SQV/r with adjusted dose of RTV (i.e., LPV/r 400 mg/400 mg twice a day or SQV/r 400 mg/400 mg twice a day).
HIV/hepatitis B virus co-infection	3TC- and/or TDF-containing regimens	AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r)

Source: WHO 2010a

Third-Line Therapy

Third-line therapy is still widely considered to be cost-prohibitive in most resource-limited settings, and it is not widely available in any of the countries reviewed for this brief. As of 2009 in low- and middle-income countries outside of the Americas, 97.5 percent of

adult patients were on first-line therapy, 2.4 percent on second-line therapy, and 0.01 percent were reported to be on third-line therapy. In the Americas, 84 percent of adults were on first-line therapy, 9.7 percent on second-line therapy, and 6.3 percent on third-line therapy (WHO 2010b). Countries reviewing WHO's 2010 recommendation that third-line regi-

mens be developed and implemented find it provides little guidance on how to obtain these drugs or what to use. For example, in Zambia third-line therapy is not supplied through the national program, although draft preliminary guidelines have recently been developed. In Honduras, third-line therapy is available on a very limited basis in the private sector, but the new national HIV strategy includes future plans for roll-out to the public sector.

The national ART program in Zambia is now in its seventh year and, as of February 2010, has already identified over 300 patients who potentially require third-line treatment. Third-line drugs are available only to patients who can afford them; the national program does not supply these drugs. However, Zambia has recently drafted preliminary guidelines on third-line therapy that recommend raltegravir (RAL) and darunavir/ritonavir (DRV/r) with either TDF/FTC or AZT/3TC. Genotyping is required before any patients are considered for third-line regimens. Because funding is not currently available, expanding access to third-line ART is on hold. However, the MOH has established a third-line advanced treatment center at the University Teaching Hospital that has the technical expertise and appropriate diagnostics to monitor patients who are able to pay for third-line regimens. Under Honduras' new HIV strategy, there are plans to offer third-line therapy at third- and fourth-level hospitals in the public sector, although it is not available yet. As of early 2011, around 8,000 patients were actively on ART through the national program, and approximately 10 patients in the country were receiving third-line therapy from abroad through a private organization.

In-country challenges with guideline implementation are summarized in Table 9.

RECOMMENDATIONS

Recognizing that the guideline process will vary in different contexts, there are a few common approaches

that have helped the countries detailed in this brief successfully adopt and implement new guidelines.

Conduct a feasibility analysis: Each country should complete a feasibility analysis of the WHO recommendations, considering the risks, benefits, costs, local values, preferences, resource requirements, and limitations of each. Robust cost forecasting can clearly articulate the human and financial resources associated with their implementation in the local context.

Include an appropriate mix of stakeholders: National health leaders should invite an appropriate mix of stakeholders to participate in the guideline revision process. It should be a forum for collaborative partnership between local and international agencies, including representatives from the government; multilateral, bilateral, and nongovernmental partner organizations; civil society; PLHIV groups; and the private sector. Technical expertise should be drawn from a mix of policymakers, program managers, implementers, clinical personnel, supply chain managers, and costing experts. Early in the revision process, efforts should be made to foster a spirit of inclusion, transparency, and technical expertise.

Strong government leadership: National health leaders should lead the revision committee to develop guidelines that will most effectively achieve their vision. Strong government leadership can dramatically reduce the timeline for guideline revision. In some cases, implementation of key recommendations can be mandated prior to dissemination of officially revised guidelines.

Establish an annual guideline review process: In the ever-changing field of HIV treatment, it is likely that recommendations will be updated or changed regularly. Establishing an annual guideline review process would significantly streamline any revisions and ensure that new WHO recommendations are automatically incorporated into country guidelines. Having a small, flexible core group of reviewers that acts as

TABLE 9. SUMMARY OF IN-COUNTRY CHALLENGES WITH GUIDELINE IMPLEMENTATION		
Country	Challenge	Description
Zambia	Stavudine (d4T) withdrawal	Phased implementation of more patient-friendly regimens over a four-year period as a result of increased up-front costs.
	Laboratory capacity	Limited use of viral load (VL) for confirmation of treatment failure due to prohibitive cost and weak laboratory capacity.
	Laboratory capacity	Limited implementation of recommendation for ART in all patients co-infected with HIV/hepatitis B virus (HBV) due to weak laboratory capacity, increased costs of HBV testing supplies, and increased antiretroviral therapy (ART) patient loads.
	ART for patients with tuberculosis (TB)	Recommends starting ART in all active TB patients within two to four weeks after starting TB treatment to manage decision point about “when to start.”
	Second-line therapy	High cost of second-line; plans for gradual transition from lopinavir/ritonavir (LPV/r) to atazanavir/ritonavir (ATV/r) due to expected cost savings.
	Third-line therapy	Developed draft third-line guidelines that recommend raltegravir (RAL) and darunavir/ritonavir (DRV/r); established third-line advanced treatment center.
Guyana	Supply chain management	Delayed implementation of more patient-friendly regimens resulting from an overstock of old antiretrovirals (ARVs).
South Africa	Supply chain management	Delayed implementation of more patient-friendly regimens resulting from lack of advance planning with ARV suppliers.
	d4T withdrawal	Health care workers switching patients to tenofovir (TDF) who do not meet eligibility criteria, adversely impacting national TDF stocks.
Nicaragua	Supply chain management	Delayed implementation of earlier ART initiation due to stockouts of CD4 reagents and problems with VL testing equipment.
Cambodia	d4T withdrawal	Exclusion of more patient-friendly regimens from revised guidelines due to prohibitive up-front costs.
	Laboratory capacity	Plans for VL scale-up hampered by prohibitive cost.
	Laboratory capacity	Exclusion of recommendation for ART in all patients co-infected with HIV/HBV from revised guidelines due to prohibitive cost and limited availability of HBV serodiagnostic and virologic tests.
	ART for TB patients	Recommends starting ART in all active TB patients within two weeks of TB treatment to manage decision point around “when to start.”
Zimbabwe	d4T withdrawal	Phased implementation of more patient-friendly regimens over a three-year period as a result of increased up-front costs.
Tanzania	d4T withdrawal	Phased implementation of more patient-friendly regimens over a three-year period as a result of increased up-front costs; health care workers switching patients to TDF who do not meet eligibility criteria adversely impacting national TDF stocks.
Honduras	Laboratory capacity	Delayed implementation of earlier ART initiation due to unavailability of CD4 testing at the primary care level.
	Laboratory capacity	Limited use of VL for confirmation of treatment failure due to four- to eight-month turnaround time for VL test results.
	ART for TB patients	Administer empirical TB treatment to suspected TB patients and monitor for clinical improvement to manage difficulty with accurate diagnosis of TB.
	Third-line therapy	New HIV strategy includes plans to offer third-line therapy through the public sector at third- and fourth-level health centers.

the standing guideline review committee will minimize costs and time associated with the guideline review process. Using email for informal correspondence and official memorandums from the MOH for formal communication will allow for more rapid adoption and dissemination of policy.

Effective supply chain management: National governments should use robust cost forecasting and commodity quantification to plan for procuring additional drugs, diagnostics, laboratory reagents, and supplies associated with the new WHO recommendations. Stocks should be monitored carefully to ameliorate the high risk of stockouts during the drug phase-in/phase-out period. Suppliers need to be informed in advance of increased demand so they can adjust their production plans accordingly. Stocks of old ARVs and their potential for expiry should be considered before disseminating new ARVs.

Develop realistic, budgeted implementation plans: As countries decide when and how to implement the WHO recommendations, they must carefully balance expansion of ART and management of program costs. A budgeted implementation plan that is time-bound and realistically considers the local context should be developed and followed carefully. A phased-in approach can be taken as necessary with certain recommendations prioritized for immediate implementation and others delayed for roll-out later. Recent data support step-by-step implementation of a revised CD4 initiation threshold first, then TDF substitution, followed by provision of second-line therapy in settings where simultaneous implementation of the recommendations is not feasible (Walensky et al. 2010a, 2010b).

Support health care workers through rapid, standardized in-service training and mentoring: Health care workers must be trained not only to deliver high-quality services according to new treat-

ment guidelines, but also to manage patient concerns associated with changes in drug regimens and dosing. Training workshops should be rolled out nationally immediately following government endorsement of revised treatment guidelines. Clear guidance around the methods and timeframe for withdrawal of d4T should be provided to health care workers. The rationale and timeframe for phased implementation of specific recommendations needs to be clearly explained in settings where such an approach is necessary. Standing implementer meetings or a similar mechanism should be established for feedback, questions, and concerns from the health care workers at the facilities to policymakers and program managers at the national level. Plans for on-the-job mentoring of health care workers during the early stages of the implementation phase should be made where possible.

Educate patients and the community: Patients need counseling to increase their understanding of the benefits associated with newer, more patient-friendly drug regimens. Patient concerns associated with changes in drug regimens, especially d4T withdrawal and dosing schedules, should be addressed. Communication with patients and the community can be achieved through targeted media messaging using printed literature, public television, and radio broadcasts, as well as through existing community structures, such as patient support groups. Media campaigns should engage and include messages from traditional and religious leaders, civil society, and PLHIV, and should reach the broadest audience possible.

Manage limited human resources through task shifting: Implementation of WHO's 2010 recommendations will result in increased patient loads for health facilities that are already under-staffed. Task shifting of ART initiation from doctors to nurses can alleviate significant bottlenecks within the HIV service delivery system. Introduction of lay health care workers to assist with patient counseling, vital sign assessments,

phlebotomy, microscopy, and administrative responsibilities should be considered.

Strengthen laboratory systems: WHO's 2010 recommendations emphasize increased laboratory screening and monitoring of HIV patients. National governments need to strengthen the capacity of laboratory systems to ensure adequate access to CD4 testing to determine ART eligibility and access to VL testing to identify treatment failure. The capacity for accurate TB diagnosis and routine HBV screening of HIV patients should be established.

Develop capacity to manage third-line therapy: As national treatment programs grow older, treatment failure becomes more widespread, and patients will increasingly require third-line therapy. National governments should develop preliminary guidelines for third-line therapy and establish centers that have the technical expertise and appropriate diagnostics to monitor patients on third-line regimens. The advent of new medications, including rilpivirine and cobicistat; the expanded use of other medications, including RAL; and the likelihood of decreased future pricing for third-line therapy precipitate the need for countries to have preliminary guidelines that will facilitate implementation of third-line therapy.

RESOURCES

This section lists key resources for countries working through the guideline revision and implementation process.

A Guide for Adaptation and Implementation: Revised Principles and Recommendations (WHO 2009): This guide was developed in late 2009 to complement *Rapid Advice* with the purpose of “assisting Member States and program managers to choose and prioritize among the recommendations, especially

where resources are limited...[and] to serve as an advocacy tool to policy makers and to provide a basis for difficult choices and decisions within Member States.”

Available at: www.who.int/hiv/topics/treatment/guide_for_adaptation.pdf

Adapting WHO Normative HIV Guidelines for National Programmes (WHO 2011): This guide “defines the principles of adaptation promoted by WHO and outlines a generic framework for the process of adapting HIV guidelines for national programs. It does not provide full guidance on developing an operational plan, but does offer suggestions for strategic planning (or re-planning) for the national response to HIV.” It also includes country case studies in the annex to offer guidance on how national programs might address some of the specific challenges being faced in the guideline adaptation and implementation process.

Available at: www.who.int/hiv/pub/who_normative/en/index.html

Crosswalk Analysis of Antiretroviral Therapy Costing Models and Their Policy Impact (AIDSTAR-One 2010): Through PEPFAR and other initiatives, several different packages of modeling software have been developed to address different aspects of resource allocation. This crosswalk analysis evaluates and compares nine commonly used ART costing models, including model utility, data output, impact on policy decisions, and other pertinent information to inform HIV policymakers and program managers.

Available at: www.aidstar-one.com/focus_areas/treatment/ART_costing_cross_walk

WHO Phase I Toolkit: Understanding the Revised WHO Recommendations and Supporting Their Adaptation into National Guidelines (Elizabeth

Glaser Pediatric AIDS Foundation 2010): This toolkit is organized into five steps that can be followed by technical partners to understand the revised WHO recommendations and provide technical guidance to countries in adapting the revised recommendations into national HIV guidelines and plans for their implementation.

Available at: www.pedaids.org/Publications/Toolkits

WHO Phase 2 Toolkit: Program, District and Facility-Level Planning for Implementation of the 2010 Revised WHO Guidelines (Elizabeth Glaser Pediatric AIDS Foundation 2011): This toolkit is organized into nine non-sequential tool sets that include various categories of implementation planning tools. In most cases, these tools consist of templates, which are frameworks to help technical partners think through program, district, and site implementation planning.

Available at: www.pedaids.org/Publications/Toolkits

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