Scaling up antiretroviral therapy in resource-limited settings: adapting guidance to meet the challenges

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Purpose of review
This review describes the evolution of WHO guidelines for antiretroviral therapy (ART) in HIV-infected individuals, considering the key epidemiological, scientific, programmatic, and political changes over the last decade, and highlights the major trends for the management of the HIV disease in future guidelines revisions.

Recent findings
In the last few years, new evidence has emerged supporting the potential preventive benefit of ART in reducing HIV transmission. This, together with the potential clinical benefits of earlier initiation of therapy, has led to the consideration of the broader strategic use of ART, taking into account the clinical and public health benefit, and programmatic feasibility.

Summary
In 2002, WHO established its first guidelines for ART use, primarily focused on a public health approach for resource-limited settings. These recommendations were updated in 2003, 2006, and 2010, incorporating progressive changes reflecting progressive increase in the knowledge of HIV pathogenesis, development of new drugs and diagnostics, and increased experience of HIV treatment and prevention programs. The impact of several international political commitments and scale-up initiatives such as the 3 by 5 Initiative, Universal Access targets, and the Treatment 2.0 Strategy were also important drivers of the global response, increasing the treatment coverage and catalyzing the necessary environment for the establishment of operational and programmatic components for an expanded and sustainable global response to HIV/AIDS.

Keywords
antiretroviral therapy, public health approach, scale-up treatment guidelines

INTRODUCTION

Ten years ago, the World Health Organization (WHO) released its first guidelines for antiretroviral therapy (ART) in resource-limited settings [1]. At that time, very few patients in low-income and middle-income countries were receiving ART. With the notable exception of Brazil, where ART was provided through the public health system since 1996 [2], most experience and evidence for using ART came from Western settings where access to specialist doctors, sophisticated laboratories, and a range of medication resulted in a patient management strategy that was considered as complex, unaffordable, and difficult to replicate in resource-limited settings, particular in sub-Saharan African countries where the need for treatment and care was greatest [3].

The first WHO ART guidelines released in mid-2002 laid the foundations for the delivery of ART within a public health framework and the limits of resource-constrained settings. Subsequent revisions of these guidelines conducted in 2003, 2006, and 2010 have adapted to the emerging clinical, operational, and programmatic challenges and changing political environment. A new revision is planned to be launched in mid-2013. This article summarizes the main themes of the four sets of ART guidelines over the last decade, framed within the political and public health challenges at the time, and reflects on the challenges ahead for future guideline revisions.

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KEY POINTS

- WHO's guidelines for antiretroviral in resource-limited settings are an important contribution to scaling up access to ART.
- Successive revisions have been based on advances in science, drug, and diagnostic development, and increased experience of HIV treatment and prevention programs.
- As treatment has been scaled up, the contribution of knowledge generated from resource-limited settings has become increasingly important.
- Future guidelines will move beyond treatment to provide recommendations on the strategic use of ART for both treatment and prevention.

2002: ANTIRETROVIRAL THERAPY AS AN URGENT LIFE-SAVING MEDICAL INTERVENTION

In 2002, less than 5% of the 6 million people estimated to be in immediate need of ART in resource-limited settings were receiving treatment. Initial reservations about the cost and complexity of delivering ART in resource-limited settings had largely given way to a growing sense of unease about the dire lack of access to ART. In the absence of treatment, average survival after progression to AIDS was less than a year [4], and the insufficiency of the global response to HIV/AIDS was described at that time as a crime against humanity [5].

The previous year had seen a growing political commitment toward HIV/AIDS. In mid-2001, the then UN Secretary General Kofi Annan described HIV/AIDS as a global problem of catastrophic proportions and called for a global alliance to be formed [6]. In the ensuing 12 months, the Global Fund to fight AIDS, Tuberculosis, and Malaria was established; the WHO Prequalification project was established to assess the quality and safety of medicines, in particular generic antiretrovirals (ARVs), and ARVs were added to the WHO essential medicines list. The US government's President's Emergency Plan for AIDS Relief (PEPFAR) was announced the following year, with an initial commitment of $15 billion over five years.

It was in this context that the first set of guidelines for ART in resource-limited settings was released. These guidelines, which were framed as 'part of the World Health Organization's commitment to the global scale-up of antiretroviral therapy' [1], were the first step toward providing a set of simplified, standardized recommendations for ART delivery in resource-limited settings, and recognized the need to provide guidance not just for individual case management, but to support a public health approach to ART delivery and scale-up. In an early reference to what was to become one of the landmark efforts in scaling up access to ART, the preface to the 2002 guidelines expressed the ambition that countries of the developing world should be able to have '3 million people on ARVs by the end of 2005'.

For HIV-infected adults and adolescents, five potential first-line regimens (including one protease-inhibitor based regimen) and eleven potential second-line regimens were put forward. The advantage of fixed-dose combinations (FDCs) was recognized, although concerns were expressed about the bioequivalence and legality of using generic FDCs. Initiation of treatment was guided by clinical criteria (WHO clinical stage 4) or clinical and immunological criteria (WHO clinical stages 1–3 and CD4 $<200/\mu l$). ART for HIV-infected children was also included as part of this first set of ART guidelines. Laboratory tests were divided into four categories: absolute minimum (i.e. HIV serology and hemoglobin), basic recommended (e.g. inclusion of white blood cell, ALT/AST), desirable (e.g. inclusion of CD4 cell count), and optional (e.g. inclusion of viral load).

2003: THE 3 BY 5 INITIATIVE

In May 2003, WHO's recently appointed Director General Dr Lee Jong-wook, in his inaugural World Health Assembly address, committed WHO to supporting the '3 by 5' target to put three million people in developing countries on ART by the end of 2005 [7]. This target had planned to be released the previous year, during the time of the previous Director General Gro Harlem Brundtland, but was delayed because of lack of donor support at that time. The 3 by 5 initiative was launched at the same time as increased global political commitment to provide funding for scale-up [8].

The next set of WHO guidelines for scaling up ART in resource-limited settings were released in 2003, just a year after the first set of guidelines, in support of the 3 by 5 initiative and in response to the new scientific data supporting the prioritization of certain ART combinations [9]. Four first-line regimens were put forward on the basis of clinical experience, availability of FDCs, lack of a requirement for a cold chain, and drug availability and cost. Drug toxicity was another consideration: stavudine (d4T), the most affordable antiretroviral available and a key component of the only three-drug generic FDC prequalified by WHO at that time, was recognized as being associated with the high frequency of long-term severe adverse events. Tenofovir (TDF),

although not part of the first-line recommendations at that time, was recognized as an effective alternative first-line option, particularly in combination with lamivudine (3TC) and efavirenz (EFV). The guidelines acknowledged that TDF could be included in the future guidelines, provided that availability and cost barriers are reduced, and that more experience in using TDF in resource-limited settings was needed. Protease inhibitors were moved out of first-line therapy and reserved as key components for second-line regimens.

Treatment initiation criteria were expanded slightly, allowing for ART initiation for patients in WHO Clinical Stage III disease with CD4 cell counts of *or less* than 350/μl. Viral load testing, while acknowledged as being too complex and costly for widespread implementation, was nevertheless recognized as an important tool for HIV programs, with the 2003 guidelines expressing hope that increasingly affordable and simplified methods of viral load will become available in the future.

As with the 2002 guidelines, there were no separate guidelines for children. Rather, children were listed as a special category of patients, together with pregnant women coinfected with active tuberculosis (TB), and injecting drug users.

2006: HIV/AIDS AS A CHRONIC DISEASE

At the end of 2005, there were just over 1.3 million people receiving ART in low-income and middle-income countries, representing a trebling in coverage in just 2 years (i.e. from an estimated 7% at the end of 2003 to 22% at the end of 2005) [10]. Most of this increase in ART coverage was accounted for by a rapid scale-up of ART in African continent, where treatment expanded more than eight-fold in just 2 years, from 100 000 at the end of 2003 to 810 000 individuals by the end of 2005. With this increased coverage came increased evidence of the impact of ART in these settings, as considerable experience began to emerge regarding clinical prognosis and challenges to expand and sustain HIV treatment and care in resource-limited settings. ART efficacy [8] and adherence [11] were found to be comparable to Western settings, although early mortality was higher [12].

While recognizing the enduring urgent need to continue improving access to ART for all in need, the 2006 ART guidelines began to acknowledge HIV as a chronic disease, requiring a long-term focus on ART affordability, strategies to support treatment adherence, retention in care, and the need to decentralize and integrate ART delivery [13].

Treatment simplification was given a boost from 2004 onwards by the prequalification of the first generic fixed-dose triple therapy combination by WHO, which helped reduce the daily ART pill burden from 10 to 15 pills to just one pill, taken twice a day. Early concerns about the potential inferiority of this generic antiretroviral combination were found to be without basis, as this combination demonstrated comparable efficacy [14]. The previous recommendation on when to start was maintained (CD4 cell count <200 cells/μl), although guidelines from Western settings were shifting toward earlier initiation [15] at or less than 350 cells/μl, and the WHO guidelines recognized that the optimum time to initiate ART with a CD4 cell count of 200–350 cells/μl was still to be established. However, cumulative experience of ART management both in Western and resource-limited settings provided greater insight into the challenges and priorities for managing ART toxicities, and this was given greater emphasis in the 2006 guidelines. Shortly after these guidelines were released, an addendum was added recommending a shift to lower dose d4T following systematic review data showing that reduced dose d4T was associated with lower rates of mitochondrial toxicity [16].

The 2006 guidelines gave special attention to hepatitis B virus (HBV), recognizing the shared transmission routes with HIV [17], and higher rates of progression to liver disease among coinfected patients [18,19]. Considerations for ART for injecting drug users (IDUs) remained a focus, but children were addressed by a separate guideline in order to support and facilitate the management and scale-up of ART in infants and children [20].

Finally, the need for simple, point-of-care assays for CD4 cell count and, in particular, viral load measurement was emphasized.

2010: EXPANDING ACCESS WHILE IMPROVING QUALITY OF CARE

2010 was a year of emerging concern about reduced financial commitment to HIV/AIDS. The global economic crisis, shifting political leadership, and competing claims from other global health priorities all threatened continued international funding support for ART scale-up [21], and for the first time since scale-up efforts began, a flat lining of HIV funding was observed.

Against this backdrop, the ART guidelines released by WHO in 2010 acted as a bold counterforce to dwindling international support and while considering economic considerations, placed evidence at the center of its recommendations. Responding to the evidence that had been generated in the 4 years since the previous set of guidelines were released, WHO issued rapid advice in late 2009 recommending earlier initiation of ART and the use

of more effective and tolerable, but more expensive regimens. Stavudine, one of the cheapest ARVs available but also the drug associated with the greatest number of toxicity-driven switches [22], was recommended to be phased out of first-line and relegated to being a back-up drug (Table 1).

Other recommendations that responded to recent evidence that had emerged since the 2006 guidelines included immediate initiation of ART for all patients with active TB disease and chronic HBV coinfection, with the need for improved HBV diagnosis and more effective treatment of HIV and HBV coinfection. Moreover, for the first time, the guidelines recommended that national programs develop policies for the third-line therapy and take a more strategic approach to monitoring for antiretroviral efficacy and toxicity, including a phasing-in approach to viral load monitoring [23].

These recommendations inevitably meant that treatment coverage targets would increase, reducing the perceived progress in scale-up efforts and requiring additional donor assistance, at least in the short term, and were thus met with resistance by some donors and affected countries. However, by 2012, the majority of countries had adapted the main recommendations in the 2010 guidelines.

FIFTEEN MILLION PEOPLE ON ANTIRETROVIRAL THERAPY BY 2015: THE CHALLENGES

In most low-income and middle-income settings, people generally initiate ART later than in industrialized countries with CD4 cell count below 200 cells/μl [24], resulting in preventable morbidity and mortality, and reduced life expectancy [25▪▪]. Particularly in the first few months after starting ART, mortality in resource-limited settings is generally higher than that observed in high-income countries [12]. The most frequently reported specific causes of death include TB, severe bacterial diseases, and cryptococcal meningitis, suggesting that most of these deaths could be avoided. The main factors associated with a risk of early mortality are immunosuppression, severe malnutrition, late stage of disease, presence of active TB when ART is initiated, anemia, and positivity of serum cryptococcal antigen.

The WHO 2010 guidelines strongly recommend earlier initiation of ART at CD4 cell count less than

Table 1. Evolution of key clinical recommendations in WHO guidelines for antiretroviral therapy over the last decade

Issue	2002	2003	2006	2010
When to start	CD4 cell count <200 cells/μl Immediate for WHO clinical stages 3 and 4	CD4 cell count <200 cells/μl Immediate for WHO clinical stages 3 and 4	CD4 cell count <200 cells/μl Consider if CD4 cell count ≤350 cells/μl Immediate for WHO clinical stages 3 and 4	CD4 cell count ≤350 cells/μl Immediate for WHO clinical stages 3 and 4, active TB disease, chronic HBV disease
First-line	5 recommended options PI options TDF potential	4 recommended options PI only for ART experienced individuals	8 recommended options (NVP or EFV) + (3TC or FTC) + (TDF or ABC; AZT or d4T) AZT or TDF preferred Move from d4T	4 recommended options (NVP or EFV) + (3TC or FTC) + (AZT or TDF)
Second-line	Boosted or non-boosted PI	Boosted PI	Boosted PI	Boosted PI (LPV/r or ATV/r preferred options)
Third-line	None	None	None	DRV/r, RAL, ETV Limited availability and high cost
CD4	Encouraged	Advisable	Advisable Need better access	Advisable Need better access
Viral load	No Not recommended Clinical monitoring only	No Encouraged	Yes Tertiary centres Need simple assays	Yes Phase-in approach

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; d4T, stavudine; DRV, darunavir; EFV, efavirenz; ETV, etravirine; FTC, emtricitabine; LPV, lopinavir; NVP, nevirapine; PI, protease inhibitor; /r, low dose ritonavir; RAL, raltegravir; TDF, tenofovir.

350 cells/μl, which has the potential to significantly reduce mortality in these settings [23], but this benefit will only be realized if strategies are found to facilitate earlier access to diagnosis and care. Thus, achieving universal access to treatment, prevention, and care implies attaining universal knowledge of HIV status. This will depend on the health system's capacity to identify those who are HIV-positive, notably at an early stage of infection, and link the newly diagnosed to effective treatment and care. Health system strengthening and community engagement are thus key elements to improving quality of care and treatment for people living with HIV in Africa.

Treatment failure remains difficult to diagnose as in most settings viral load and drug resistance tests are not readily available. There are several arguments that support a greater investment to support improved access to viral load. First, early diagnosis of treatment failure can support strategies for treatment adherence; studies from resource-limited settings have found that, in the majority of instances, patients with a high viral load will resuppress after an adherence intervention [26,27]. Second, the alternative approach of diagnosing treatment failure based on immunologic and clinical results is inaccurate and may result in switching unnecessarily to second-line therapy [28▪]. Third, because virologic failure precedes immunological and clinical failure, using CD4 count criteria for switching treatment regimens implies continuation of ineffective treatment for a longer period of time and therefore an accumulation of nucleoside reverse transcriptase inhibitor (NRTI) resistance, which will affect the limited choices for NRTI use in the second-line regimens. Fourth, existing cost-effectiveness models suggest that this intervention can be cost-effective when used to reduce or limit the number of CD4 monitoring tests that are done [29▪▪]. Finally, virological suppression is an important measure of an individual's risk for transmitting HIV.

Although potentially cost-effective over time, plasma viral load still currently remains too expensive for wide-scale implementation in most resource-limited settings. Nevertheless, just as the case was made to increase access to treatment in 2002 despite cost concerns, if the 2010 WHO guidelines are to move beyond wishful thinking, then efforts are needed to reduce the price of reagents and equipment [30]. Technological and logistical challenges linked to viral load testing make its decentralization complex, especially in rural areas. It is anticipated that improvements will come shortly as an increasing number of point-of-care viral load technologies become available.

Improvements in access to tools to detect treatment failure will require commensurate improvements in access to second-line and third-line drugs. Currently, second-line drugs are poorly available, while third-line drugs are not routinely available because of the limited ability to detect early failure and higher cost of drugs [31]. The result is that substantial numbers of patients have already failed first-line ART without receiving adequate treatment. Consequently, it has been observed that countries where routine viral load and second-line therapy are available have lower mortality in HIV programs compared to countries where access is limited [32▪].

Both ritonavir-boosted atazanavir and ritonavir-boosted lopinavir are the currently preferred protease inhibitor options for second-line regimens recommended by the WHO. Heat-stable boosted lopinavir remains the most commonly prescribed protease inhibitor in second-line regimens in resource-limited settings [33]. In the absence of genotype testing and considering the amount of time spent under a failing first-line regimen, optimizing the choice of the NRTI backbone associated with the protease inhibitor remains a challenge. It is likely that many second-line treatments currently offered in sub-Saharan African countries are suboptimal in this regard.

Designing and implementing specific studies in relation to third-line regimens to assess the needs and define the most appropriate regimens for resource-limited settings are important priorities. The WHO guidelines currently recommend ritonavir-boosted darunavir, raltegravir, and etravirine as third-line options [23]. At current prices, their cost would be up to 10 times that of the recommended second-line regimens [34]. Again, depending on resistance patterns, the choice of drugs for the NRTI backbone will be an important consideration. Moreover, resistance to new drugs is a particular challenge for third-line regimens: resistance to etravirine could be more frequent than expected in settings in which patients remain with non-nucleoside reverse transcriptase inhibitor (NNRTI)-based potentially failing first-line regimens for a long period of time; resistance to protease inhibitors, although potentially less frequent, could be an important issue in view of recycling protease inhibitors and saving darunavir.

LOOKING AHEAD: THE STRATEGIC USE OF ANTIRETROVIRAL THERAPY FOR TREATMENT AND PREVENTION

The most significant evidence to have emerged in the field of ART in recent years has come from the HPTN 052 trial which demonstrated that ART can

significantly reduce HIV transmission by up to 96% among people in HIV serodiscordant relationships [35▪▪]. Other important advances include the use of ARVs in preexposure prophylaxis and accumulating evidence on the potential clinical benefit of ART initiation above 350 cells/μl.

As well as catalyzing renewed engagement toward further improving access to ART, the focus on treatment as prevention in recent years has encouraged increased attention to improving ART delivery along the cascade of care from HIV testing to long-term retention [36]. The 3 by 5 initiative launched a decade ago rightly focused on increasing the number of people in ART. Today, there is a clear recognition that more attention needs to be paid identifying and implementing supportive strategies to improve uptake of HIV testing, assessment of treatment eligibility, rapid initiation of ART, and long-term adherence and retention in care. Evidence from recent systematic reviews have found high rates of patient attrition along the cascade of care, from testing to treatment [37,38], and although recent efforts have been made to identify strategies to improve linkage to care [39▪], adherence to treatment [40], and retention in care [41], much more remains to be done.

The accumulating evidence supporting the treatment and prevention benefits of earlier ART initiation have raised important questions for recommendations regarding when to start ART. In 2011 and 2012, WHO convened two expert consultations on the strategic use of ARVs for the treatment and prevention of HIV [42,43]. These consultations were designed with the aim of informing the scope and content of WHO's next set of ART guidelines, to be released in mid-2013. These guidelines will provide consolidated guidance on the strategic use of ARVs in three areas. First, clinical considerations, such as the evidence for clinical benefit in terms of mortality and morbidity reduction, and also public health benefits in terms of reduced incidence of HIV, TB, and other infections. Second, operational considerations, in particular regarding the model of care delivery (decentralization, task shifting, and integration) that can be supportive of expanding access to ART. And third, the programmatic considerations prioritizing between a range of potential options for the strategic use of ART in different epidemiological and economic environments (e.g. high fertility rates favoring early lifelong ART for pregnant women in certain contexts) (Fig. 1).

CONCLUSION

WHO's guidelines for ART provide important recommendations, both for resource-limited settings and globally. Although the recommendations

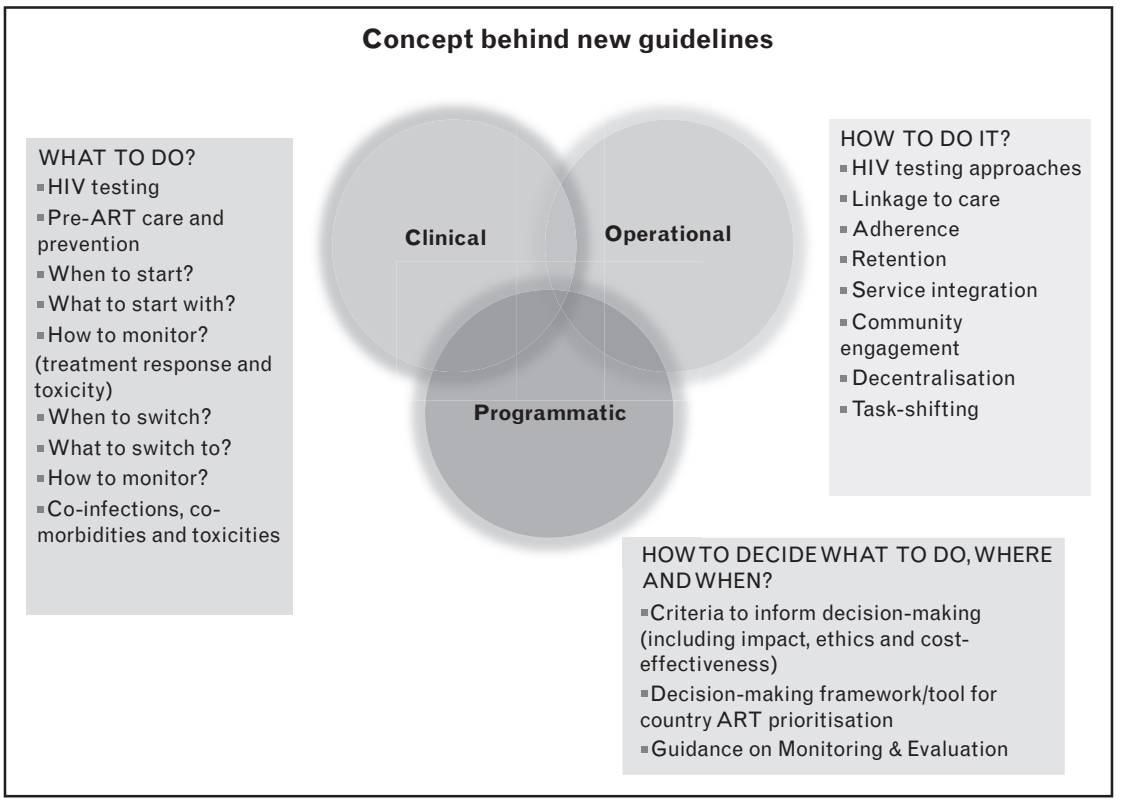

FIGURE 1. Consolidation of clinical, operational, programmatic guidance.

are firmly rooted in updated assessments of the evidence base, they also reflect the political and programmatic challenges faced in striving for the goal of universal access to ART. While aiming for simplicity, the guidelines have always striven to recommend the best possible standard of care within a public health approach. This means acknowledging the importance of certain key technologies and strategies that may be beyond the reach of resource-limited settings but which nevertheless are desirable for optimal patient care. In this way, WHO's ART guidelines are more than just technical documents: they set forth not only the minimum standard for today, but also what should be the ambitions for the future.

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Conflicts of interest

None.

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- ■ of special interest
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