The 2013 WHO guidelines for antiretroviral therapy: evidence-based recommendations to face new epidemic realities

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Purpose of review
The review summarizes the key new recommendations of the WHO 2013 guidelines for antiretroviral therapy and describes the potential impact of these recommendations on the HIV epidemic.

Recent findings
The 2013 WHO guidelines recommend earlier initiation of antiretroviral therapy (ART) at CD4 500 cells/μl or less for all adults and children above 5 years. Further recommendations include initiation of ART irrespective of CD4 cell count or clinical stage for people co-infected with active tuberculosis disease or hepatitis B virus with severe liver disease, pregnant women, people in serodiscordant partnerships, and children under 5 years of age. The ART regimen comprising a once daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine) + efavirenz is recommended as the preferred first-line therapy. Several approaches are also recommended to reach more people and increase health service capacity, including community and self-testing, and task shifting, decentralization, and integration of ART care.

Summary
If fully implemented, the 2013 WHO ART guidelines could avert at least an additional 3 million deaths and prevent close to an additional 3.5 million new infections between 2012 and 2025 in low- and middle-income countries, compared with previous treatment guidelines.

Keywords
antiretroviral therapy, public health approach, simplification, strategic use

INTRODUCTION

When the WHO issued its first antiretroviral therapy (ART) guidelines for resource-limited countries at the end of 2002, about 300 000 people in such settings were receiving HIV treatment. The majority of people in need of treatment at that time were unable to access it, particularly in high-burden countries in sub-Saharan Africa where HIV was the leading cause of death. Globally, around 2.4 million people were estimated to have died of HIV-related causes that year [1].

Ten years later, at the end of 2012, some 9.7 million people were receiving ART in low and middle-income countries. Over this period, the scale-up of ART had averted an estimated 4.2 million deaths in low- and middle-income countries in the previous decade [2▪]. Currently, with a more effective treatment, people living with HIV can be expected to live a near-normal life expectancy [3▪▪,4].

Recent evidence has also demonstrated the impact of ART in preventing HIV transmission [5,6▪▪], especially when ART is combined with other prevention interventions. A recent modelling study estimated that a combination of HIV prevention interventions and ART coverage of 80% or higher (at CD4 ≤350 cells/μl) could half the number of annual new HIV infections globally from more than 3 million to 1.3 million by 2025 [7]. Further studies

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KEY POINTS

- The 2013 WHO consolidated guidelines for ART aim to further simplify ART delivery while maintaining a high standard of quality of care.
- Key new recommendations include a move towards earlier initiation, at CD4 500 cells/μl or less, and immediate ART for certain populations.
- These recommendations can be expected to prevent an additional 3 million deaths by 2025.
- Substantial reductions in new HIV infections are also anticipated.

have indicated a role for antiretrovirals as pre-exposure prophylaxis for HIV-negative individuals, provided that high adherence levels can be achieved [8].

The growing appreciation of the clinical and preventive benefits of ART, together with increased availability of safer and more effective treatment regimens, has led to an evolution in global guidance towards earlier initiation of ART for clinical benefit, and immediate initiation of ART for certain populations for the prevention of ART transmission [9].

This article summarizes the main recommendations of the WHO 2013 guidelines for ART provision, the potential impact for countries in terms of costs and benefits, and provides a perspective for future guidance.

WHO 2013 GUIDELINES FOR ANTIRETROVIRAL THERAPY INITIATION

The main new recommendations for ART initiation focused on two questions: when to start ART and what drugs to start with.

When to start

Over the past decade, as evidence has evolved and new drugs with better safety profiles have become available, guidelines of the WHO [9] and those of developed and developing countries [10] have moved towards earlier initiation of ART at higher CD4 cell counts.

The last set of WHO guidelines for ART for adults and adolescents issued in 2010 recommended initiating ART for all individuals with a CD4 cell count 350 cells/μl or less, regardless of WHO clinical stage and for those with severe or advanced HIV disease (WHO clinical stages 3 or 4) regardless of CD4 cell count [11].

Since 2010, evidence and programmatic experience have continued to shift the benefit–risk ratio towards initiating ART earlier. Two randomized trials [6▪▪,12] provided evidence supporting earlier initiation of ART to reduce mortality, and this was further supported by evidence from numerous observational cohort studies [13–16]. Further evidence, also from cohorts, suggests that untreated HIV may be associated with the development of several non-AIDS-defining conditions including cardiovascular disease, kidney disease, liver disease, some cancers, and neurocognitive disorders [17,18].

In July 2013, following a review of the available evidence, WHO issued a new set of ART guidelines that recommended earlier initiation of ART at CD4 cell count 500 cells/μl or less for all adults and children above 5 years. Further recommendations were included to initiate ART immediately (i.e. irrespective of CD4 cell count or clinical stage) for certain patient groups including people co-infected with active tuberculosis disease or hepatitis B virus infection with severe liver disease. These recommendations were based on evidence of clinical benefit.

Three additional recommendations to provide immediate ART initiation in pregnant women, people in serodiscordant partnerships, and children under 5 years of age were also made, based on clinical benefits as well as programmatic and prevention considerations. For pregnant women, the main rationale for the recommendation was to harmonize recommendations for the prevention of mother-to-child transmission (PMTCT) with treatment of adults in general, enrol more pregnant women onto treatment, and reduce the risk of lost of follow-up, mainly because of confusion caused by stopping and restarting treatment in settings of high fertility rates [19]. The recommendation to provide lifelong ART to all pregnant and breastfeeding women with HIV or to continue ART only for those meeting treatment eligibility criteria for the woman's health is conditional, based on the epidemic setting and programme considerations, recognizing the absence of conclusive evidence on the impact and efficacy of fully implementing lifelong ART.

For HIV-serodiscordant couples, immediate initiation of ART is recommended, mainly to prevent onward transmission of HIV to the sero-negative partners. This recommendation was based on the results of the HPTN052 study that provided strong support for use of ART to prevent HIV transmission among HIV-serodiscordant couples [6▪▪].

For children below the age of 5 years, the 2013 guideline recommendation for immediate initiation

of ART is based on the recognized need to simplify criteria for initiating ART in children to improve treatment coverage and reduce mortality. Similarly, for programmatic purposes and given that disease progression in children 5 years and older is comparable to that of young adults, alignment with ART initiation criteria for adults was recommended (i.e. ART initiation at CD4 cell count $\leq$500 cells/μl).

What to start

Recommendations for when to start ART require a trade-off between benefits and risks for patients. The main clinical risks associated with earlier initiation of ART relate to prolonged exposure to drug toxicities.

The 2010 WHO guidelines recommended a move away from stavudine as part of first-line ART based on the accumulating evidence that long-term exposure to stavudine has the potential to cause disfiguring, painful, and life-threatening side effects, such as lipodystrophy, peripheral neuropathy, and lactic acidosis [20–22]. A choice of one non-nucleoside reverse transcriptase inhibitor was recommended (either nevirapine or efavirenz), to be combined with two nucleoside reverse transcriptase inhibitors (either tenofovir or zidovudine) combined with lamivudine or emtricitabine.

Several systematic reviews carried out in support of the 2013 WHO guidelines have given preference to an antiretroviral regimen composed of a once daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine) + efavirenz as single preferred first-line therapy. Tenofovir and efavirenz are recommended in recognition of their more favourable safety profiles compared with zidovudine and nevirapine [23,24]. Lamivudine and emtricitabine are considered pharmacologically equivalent, and either can be used depending on availability and affordability [25,26].

For pregnant women, additional consideration was given to the evidence regarding safety of efavirenz in pregnancy. Early preclinical data and case reports suggested an association between efavirenz exposure and an increased risk of neural tube defects, and previous guidelines have cautioned against the use of efavirenz in the first trimester of pregnancy. However, more recent systematic reviews have found no evidence of an increased risk of either birth defects overall or neural tube defects [11], and while more data are needed, the evidence to date provides reassurance that efavirenz can be used throughout pregnancy [27]. The same recommendation regarding what to start in adults, therefore, applies equally to pregnant women.

For children, lack of safety data and appropriate paediatric formulations limit the use of tenofovir and efavirenz. Below 3 years, new evidence has become available for this age group suggesting the superiority of a boosted liponavir-based regimen over a nevirapine-based regimen regardless of PMTCT exposure [28,29]. Above 3 years of age, it is recommended that children are switched to efavirenz-based regimens in alignment with adults.

TREATING MORE PEOPLE, EARLIER: OPERATIONAL GUIDANCE TO SUPPORT SCALE-UP

The successful scale-up of ART has led to a steady increase in the median CD4 at treatment initiation over the past decade, but still the majority of people in low- and middle-income countries initiate treatment late, at median CD4 cell count values lower than 200 cells/μl [30]. Whereas the evidence suggests that treating people earlier in their infection is beneficial from both clinical and public health perspective, these benefits will not be realized without adaptations in approaches to service delivery and the establishment of more effective approaches and policies to reduce stigma.

HIV testing is the critical first step in linking people living with HIV to appropriate care. The WHO 2013 guidelines provide several recommendations to support earlier identification and treatment of people who are HIV-positive. Strategies that have been demonstrated to work in a range of settings include provider-initiated testing in antenatal services [31], tuberculosis, and other services, couple testing (i.e. routine offer of tests partners of HIV-positive individuals) [32], home-based testing [33▪], and self-testing [34].

Once people are diagnosed as HIV-positive, it is important to ensure that they can be effectively linked to care. Recent studies have shown substantial rates of attrition along the care pathway from HIV testing to assessment for treatment eligibility to initiation of ART, for both adults [35] and children [36▪]. Several interventions have been shown to improve outcomes for pre-ART patients, including quality counselling, the provision of isoniazid and co-trimoxazole prophylaxis, various methods to encourage regular visits (such as transport allowances), and approaches that shorten the pre-ART period [37▪]. For pregnant women, the recommendation to start all HIV-positive pregnant women on ART and continue for life irrespective of immune status is already demonstrated to lead to rapid

increases in the number of pregnant women being enrolled onto ART [38].

The anticipated increase in the number of people on ART will require adaptations in the way treatment is delivered and maintained. The 2013 guidelines recommend several approaches to increase health service capacity, including task-shifting of ART delivery from clinicians to nurses and other non-physician clinicians [39], decentralization of ART delivery from hospitals to health services [40▪▪], community ART delivery [41], and integration of ART care into other health services [42▪▪,43].

PROJECTED COSTS AND BENEFITS OF THE 2013 RECOMMENDATIONS

The WHO 2013 recommendations for earlier initiation of ART for the treatment and prevention of HIV will lead to a substantial increase in the number of people considered eligible for ART. Over the medium term, this is expected to lead to substantial reductions in mortality and incidence.

Initiating ART earlier, as recommended in the 2013 WHO ART guidelines, could prevent an additional 3 million people from dying between 2012 and 2025, compared with previous initiation criteria [2▪].(Fig. 1).

Substantial reductions in new HIV infections are also anticipated. The new recommendations could, if fully implemented, prevent close to an additional 3.5 million new infections between 2012 and 2025 in low- and middle-income countries, compared with previous treatment guidelines. (Fig. 2). Further reductions in the number of people acquiring HIV infection depend on the scale and effectiveness of the existing array of prevention interventions, the use of new interventions such as pre-exposure prophylaxis of HIV, and the potential development of new prevention technologies [2▪].

Fully implementing the 2013 WHO ART guidelines would expand the pool of people eligible for ART globally to a potential 25.9 million people, compared with 16.7 million under the 2010 guidelines by the end of 2012. Progressively scaling up ART will require increased funding, but the anticipated reductions in mortality and infection will also generate greater returns. Assuming that ART coverage increases gradually to about 80% of the total number of people eligible for treatment, total annual investment in the entire global HIV response in 2025 would need to increase by just 10%, from US$ 22 to 24 billion under the previous guidelines [7]. These resource needs are projected to level-off over time before declining after 2025, a trend that reflects the accumulated prevention benefits of expanding ART provision. Further cost savings can be achieved through various programme adaptations and efficiency gains, including decentralization, reduced clinical visits, task shifting, and the

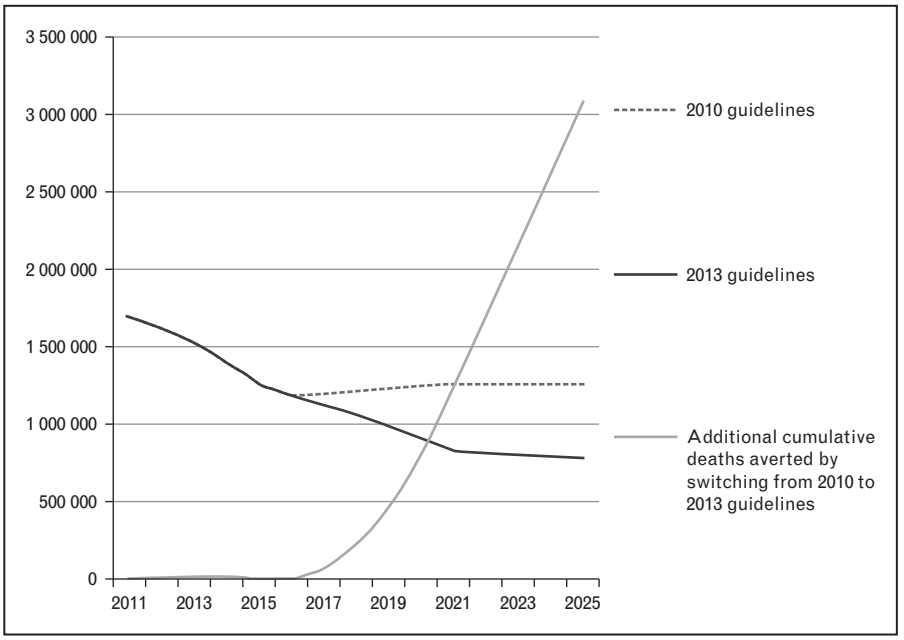

FIGURE 1. Number of projected annual deaths averted comparing WHO 2010 and 2013 guideline recommendations for ART initiation.

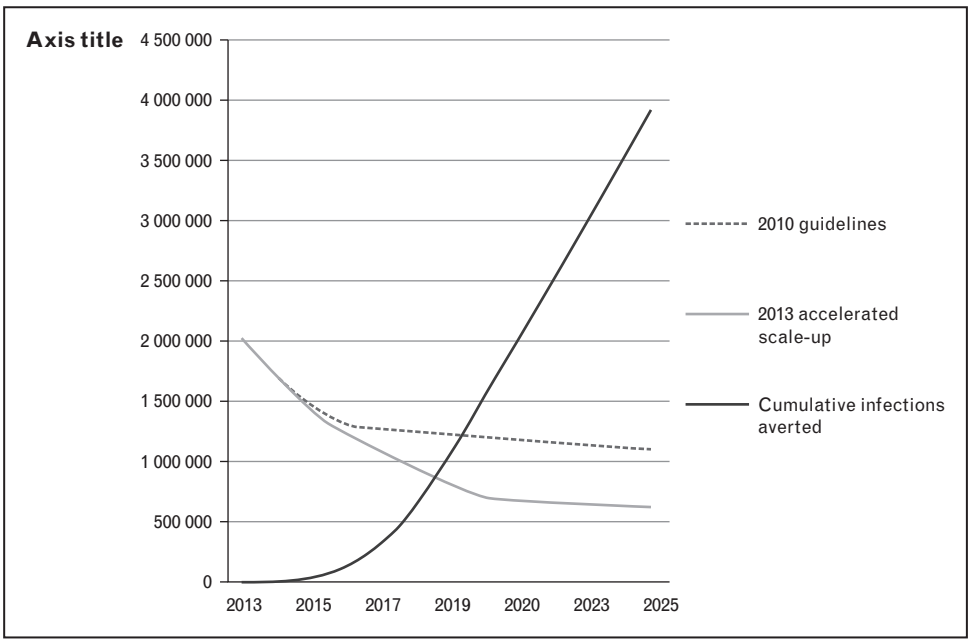

FIGURE 2. Projected annual HIV incidence and infections averted comparing WHO 2010 and 2013 guideline recommendations for ART initiation.

devolution of ART activities to community-based services. There are also potential cost savings on medicines as generic drugs and fixed-dose combinations become more widely available, economies of scale increase and through treatment optimization to reduce the doses of active pharmaceutical ingredients used in ART medicines, provided robustness is maintained.

FUTURE DIRECTIONS: TOWARDS UNIVERSAL ANTIRETROVIRAL THERAPY

Previous guidelines for ART initiation have based recommendations primarily on evidence of individual clinical benefit. Up to 2010, a CD4 threshold of 200 cells/μl was recommended for low and middle-income settings based on cohort data showing that HIV disease progression and death are greater in individuals starting ART at CD4 cell count 200 cells/μl or less [44]. Since then, several studies have indicated a clinical benefit of earlier initiation at higher CD4 thresholds, leading some clinical guidelines to recommend that patients be offered ART irrespective of CD4 cell count, on the basis of expert opinion [45].

The strategic use of antiretrovirals for treatment and prevention of HIV infection expands the range of options for offering ART, introducing additional dimensions of earlier initiation to simplify ART delivery to prevent onward HIV infection. The extent to which early initiation of ART (i.e. above CD4 500 cells/μl) can reduce infection in other populations is a matter of debate [46], but this approach is already being explored through modelling studies for certain populations at high risk of infection and transmission such as people who inject drugs [47] and men who have sex with men [48].

These considerations will likely lead to a continued policy evolution towards earlier initiation of ART such that, in the future, it may no longer make sense to triage people based on a multiplicity of clinical and laboratory criteria in order to delay treatment initiation for a minority of people.

CONCLUSION

The past decade has seen a growing appreciation of the multiple benefits of ART to reduce mortality, prevent illness, and reduce onward transmission of HIV, and this evolution has been reflected in successive ART guidelines. The next decade will likely see a further expansion in eligibility criteria for treatment initiation, with an increasing number of countries moving towards a 'test-and-treat' approach. To support this shift, implementation science will be critical to validate approaches to help identify people as early as possible after HIV infection, maximizing early ART uptake and supporting long-term adherence.

Acknowledgements

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Conflicts of interest

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