Developing the 2013 WHO consolidated antiretroviral guidelines

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Introduction

The 2013 'Consolidated guidelines on the use of antiretroviral (ARV) drugs for treating and preventing HIV infection' [1], released in July 2013, are the latest and most comprehensive of a series of important guidelines on antiretroviral therapy (ART) over the last decade from the World Health Organization (WHO). They were developed in response to important advances in the science and practice of HIV care since publication of the 2010 WHO guidance for adults and adolescents [2], pregnant women [3] and children [4]. This includes evolving evidence on the preventive and individual clinical benefits of earlier ART, innovations in service delivery such as the progressive decentralization of HIV testing and care, and the more widespread availability and affordability of once-daily fixed-dose combinations (FDCs) ART regimens [5].

In this special supplement of AIDS, we present a series of thirteen articles and five commentaries covering key aspects of the consolidated guidelines: the process, evidence base, recommendations and guidelines implementation. In this first article, we describe the WHO process and methodology of developing these guidelines. This is followed by seven selected systematic reviews [6–12] that provided the evidence base for specific recommendations. They are presented under the section heading of the relevant guidelines population or topic: Adults and adolescents (when to start ART) [6]; Pregnant women (safety of efavirenz in pregnant and breastfeeding women) [7]; Children (what ART regimen to use in children under 3 years) [8]; ART monitoring (how to monitor treatment response in adults and children) [9,10]; Service delivery (evaluation of effectiveness of service delivery innovations of decentralization and integration) [11]; and different strategies to improve treatment adherence [12]. The systematic reviews in each section are prefaced by commentaries written by the co-chairs and/or members of the Guideline Development Groups (GDGs) that highlight key recommendations and their rationale, and provide additional context for guidance [13–17]. The International HIV/AIDS Alliance and the Global Network of People Living with HIV (GNP+) report on the findings (and lessons learnt) from their consultation on community values and preferences that also informed many of the recommendations [18]. The three concluding articles all address different aspects of the critical phase of country-level adaptation and implementation of the guidelines. This includes what is known about the current status of national adoption of the recommendations in WHO ARV guidelines [19], projections of the global impact and cost of implementation of new recommendations [20] and country-level implications of implementing these guidelines for policy makers, such as diversification of service delivery models, generation and use of data, healthcare financing, human resource capacity and supply chains for drugs and diagnostics [21].

This supplement is not intended to be an exhaustive collation of all the evidence that informed the consolidated guidelines. Several of the commissioned systematic reviews as well as modelling studies have already been published in the peer reviewed literature or are in development [22–28], and a companion AIDS supplement published in January 2014 has already collated other modelling work that contributed to the guidelines process [29]. A comprehensive summary of all supporting evidence is provided as Web Annexes in the guidelines website (http://www.who.int/hiv/pub/guidelines/arv2013/annexes/en/index.html).

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Distinctive features of the 2013 WHO consolidated guidelines

The 2013 consolidated guidelines were distinctive from previous WHO ART guidelines, or other international ART guidelines in several ways.

Providing guidance across the entire continuum of HIV care

More than fifty new recommendations are provided across the cascade of HIV care, from HIV testing and diagnosis, linkage to care, using ART for prevention, ART initiation, monitoring for treatment failure and ART toxicity, and retention in care. This comprehensive approach responds to the needs of programme managers who are responsible for delivery of care across all of these steps.

Expanding guidance: clinical, operational and programmatic

In addition to the usual clinical recommendations, there is operational guidance on how to improve delivery of HIV care (with recommendations on task shifting, decentralization, integration and adherence and improving retention in care). The guidelines also provide a framework and tools for programme managers to consider in prioritizing implementation of recommendations according to their national context, including HIV epidemiology, levels of ART uptake, health workforce capacity and available financial resources. This integrated approach better reflects the complex interplay between clinical recommendations and implementation at facility and programme level.

Addressing all ages and populations

Instead of separate ART guidelines for adults, pregnant women, adolescents and children, as in previous years, guidance is provided across all age groups and populations of adults, pregnant and breastfeeding women, adolescents, and children, as well as those coinfected with tuberculosis (TB), hepatitis B and/or hepatitis C. This enables a more harmonized approach to ART regimen choice, simplifying both the role of healthcare providers, and procurement and supply chain management.

Target audience: programme managers in low-income and middle-income countries

As for other WHO guidelines, the primary target users are country policy makers and programme managers responsible for national and regional policy and planning decisions on ART scale-up, and in settings with limited resources.

Incorporating the key guiding principles of the public health approach and health equity in ART scale-up

The 2013 guidelines, as with previous WHO ART guidance, are based on a public health approach to ART scale-up that promotes simplified and standardized approaches to treatment and monitoring that facilitates the widest possible access to high-quality care at the population level [30]. This in turn requires innovations in service delivery to maximize the efficiency of HIV programmes such as through integration of HIV care with other services (e.g. maternal and child health, TB and drug dependence), improved treatment adherence and retention in care, harmonized ART regimens and more affordable diagnostics. Another key guiding principle underpinning implementation of the guidelines is promotion of human rights and health equity in national HIV policies and programmes, so that expanded access is fair and equitable; priority for ART initiation is given to those most in need; and care is provided in a supportive and responsive environment, free of stigma and discrimination.

Linking new recommendations with existing guidance

New recommendations on the use of ART for treatment and prevention have been harmonized with relevant selected recommendations from existing WHO guidance on HIV testing, prevention and management of coinfections.

WHO guidelines development process and the GRADE approach

The revision process for the 2013 guidelines was initiated in early 2012, and conducted in accordance with procedures established by the WHO Guidelines Review Committee, to ensure that WHO guidelines are developed using a transparent, evidence-based, decision-making process [31]. Since 2008, WHO has used the internationally agreed standard of the GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) to assess the quality of a body of evidence, formulate recommendations and rate their strength [32–38] (GRADE working group: http://www.gradeworkingroup.org).

Quality of evidence and strength of recommendation

GRADE classifies the quality of evidence into one of four levels: high, moderate, low and very low. The rating of quality of evidence from randomized controlled trials starts as high, but may be decreased because of risk of bias, inconsistency in results across studies, indirectness of evidence, imprecision and publication bias [34–36]. The rating of evidence based on observational studies starts as low, but may be increased if the magnitude of the treatment effect is very large, there is evidence of a dose–response relationship, or if residual biases would underestimate the effect size [37]. In addition to the quality of

the evidence, other considerations in formulating recommendations and rating their strength include the overall balance of benefits and harms to the individual and at a population level, community values and preferences, resource use, cost-effectiveness, feasibility and constraints to implementation in multiple settings, equity and human rights implications [38] (Table 1).

GRADE also classifies strength of recommendations as either 'strong' or 'conditional' [38]. A strong recommendation is one for which the GDG was confident that the desirable effects of the recommendation outweigh the undesirable effects, while a conditional recommendation is used when it is concluded that the desirable effects probably outweigh the undesirable effects, but there is uncertainty about these trade-offs. The higher the quality of evidence, the more likely a strong recommendation can be made. A conditional recommendation is more likely when high-quality evidence is absent, the estimates of effect are imprecise, there is uncertainty or variability in how individuals value the outcomes, or the benefits are either small or not considered worth the costs. The implications of a conditional recommendation are that, although most people or settings would adopt the recommendation, some would do so only under certain conditions.

The following sources of evidence and supporting material were used to inform the development of the new recommendations.

Systematic reviews

Systematic reviews were commissioned on forty-six topics across the continuum of HIV care, including nine on when to start ART; eleven on what ART to start; four on monitoring the response to ART; six on monitoring toxicity; and eleven on operational aspects of service delivery. The questions were framed using the Population, Intervention, Comparison and Outcome (PICO) format [33], and outsourced to seven different research teams and organizations through a process of competitive tendering. These groups then developed search protocols and conducted reviews of the available scientific evidence. A standardized GRADE evidence table was used to present quantitative summaries of the evidence and assessment of its quality for each PICO question by outcome [32]. The full list of review questions, search protocols, GRADE tables and evidence summaries for each topic are available at http://www.who.int/hiv/pub/guidelines/arv2013/annexes/en/index.html.

Seven systematic reviews are included in this supplement [6–12], and others have been published elsewhere [22–28], or are in development.

Consultations on community values and preferences

An assessment of community values and preferences on key ARV guideline topics was coordinated by the International HIV/AIDS Alliance and the Global Network of People Living with HIV (GNP+) through both an online e-survey ($n = 1088$), and moderated e-forum discussions with civil society networks ($n = 955$) [18,39] in six languages (Arabic, Chinese, English, French, Russian and Spanish). Key topics included community preferences regarding possible recommendations (e.g. which ART regimens to use and when to initiate ART for adults, adolescents, pregnant and breastfeeding women, and children), as well as ART service delivery considerations. Four focus group discussions were also held in Uganda and Malawi on the experiences of pregnant women with lifelong ART (option B+). Finally, two e-surveys of health workers caring for HIV-infected adults ($n = 98$) and children ($n = 342$) were undertaken on similar topics covered in the community consultation through clinical networks of eight global implementing partner organizations. In addition to the report in this supplement [18], a full consultation document is available [39].

Mathematical modelling of impact and cost effectiveness

We commissioned two key modelling projects on health impact (measured using disability-adjusted-life-years

Table 1. Key domains considered in formulating recommendations and determining their strength (strong or conditional).

Domain	Rationale
Quality of the evidence	The higher the quality of evidence, the more likely that a strong recommendation is warranted.
Benefits and risks	Desirable effects (benefits) need to be weighed against undesirable effects (risks). The more that the benefits outweigh the risks, the more likely that a strong recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely a conditional recommendation is warranted.
Values and preferences (acceptability)	If a recommendation is likely to be widely accepted or highly valued, the more likely a strong recommendation is warranted. The greater the variability or uncertainty in values and preferences, the more likely a conditional recommendation is warranted.
Costs (resource use)	The higher the costs of an intervention, especially if there is a small net benefit, the less likely a strong recommendation is warranted. Lower costs (monetary, infrastructure, equipment or human resources) or greater cost-effectiveness will more likely result in a strong recommendation.
Feasibility	If an intervention is achievable in a setting in which the greatest impact is expected, the more likely a strong recommendation is warranted.

(DALYs)) and cost-effectiveness from the HIV Modelling Consortium (www.hivmodelling.org) to support the 2013 guidelines. The first examined various HIV testing strategies and criteria for ART initiation in different populations (adults, pregnant women and HIV serodiscordant couples) on the basis of data from countries representative of different HIV epidemic types (generalized, concentrated and mixed) and level of ART coverage [26]. A second project examined different strategies for monitoring treatment response (clinical, $CD4^+$ T-cell count and viral load) and switching to second-line ART [27]. A key strength of these analyses was their use of multiple independently developed models to compare different scenarios, for which there were limited data in the literature. Additional modelling work commissioned included a causal modelling analysis of the impact of starting ART at different ages in children, based on data from the IeDEA South African collaboration [28]. A recent article has highlighted some of the challenges in using modelling data in guidelines development, including the lack of standardized criteria for rating the quality of modelling, and clarity on the positioning of modelling within the GRADE framework for decision-making [40]. It concludes with some key considerations to guide the future use of modelling in guidelines development.

Feasibility surveys

Reports were commissioned on country implementation experiences, including adoption of lifelong ART in pregnant and breastfeeding women (option B+) in Malawi; introducing tenofovir (TDF) in first-line ART regimens in Zambia; phasing out stavudine (d4T) in Zimbabwe; and scaling up viral load monitoring in Médecins Sans Frontières programmes in southern Africa. These are summarized in the consolidated guidelines web annexes (http://www.who.int/hiv/pub/guidelines/arv2013/annexes/en/index.html).

Impact assessment of implementation of recommendations

An impact assessment was undertaken using the AIDS Impact Model (AIM) and Goals model within the Spectrum modelling system [41] to estimate the number of adults and children newly eligible for ART, based on the new treatment recommendations [20]. It also examined the cost and impact that would result if ART coverage expanded to 80% of those eligible for ART.

End-user survey to inform guidelines presentation and dissemination strategies

An additional preparatory activity was the conduct of an internet-based survey of country-level end-users of recent WHO HIV-related guidelines. This was undertaken to understand better how WHO ART guidelines are used, and identify areas for improvement in format, presentation and dissemination of the new guidelines. The survey targeted WHO National Program Officers and Ministry of Health HIV focal persons, and was administered in English, French, Russian and Spanish between June and September 2012. Overall, there were 78 respondents from 44 countries across all regions (28% South East Asia and Western Pacific, 26% from Central and Eastern Europe, 10% Latin America and Caribbean, 28% Sub-Saharan Africa, 8% Middle East). All respondents had used at least one of twelve WHO HIV guidelines, and the majority (75%) had used them primarily in the development of national guidelines. Although the response rate was limited, and not fully representative of all end-users, there was a good geographic spread of respondents, and several consistent observations emerged. There was a broad agreement that the most critical guideline components were clearly stated recommendations with brief evidence summaries and a clear rationale supporting the recommendation (with inclusion of GRADE tables only as part of web annexes). The value of best practice examples from a wide range of different settings to support implementation was also highlighted. Specific suggestions to enhance readability included reduced length, larger font size, and greater use of colour, summary tables and algorithms. Accessibility and user engagement in dissemination of new WHO HIV guidelines were highlighted as critical factors influencing effective country-level adaptation and implementation. Specific activities to facilitate regional and country-level dissemination of the guidelines activities were in-country workshops and webinars; the availability of guidelines in all UN languages, particularly Arabic, Chinese and Russian; the continued need for printed in addition to electronic versions of the guidelines; and an improved notification system for new guidelines using e-mail together with conference and website announcements.

Guideline development groups (GDGs) and process of formulating recommendations

The development of recommendations was undertaken by four separate, external technical GDGs: Adult; Maternal and Child Health; Operational and Service Delivery; and Programmatic, but managed as a unified process to ensure an integrated guidelines document for adults, pregnant and breastfeeding women and children. There were more than 112 GDG members across the four groups, comprising HIV clinicians, researchers, country HIV programme managers, guideline methodologists, partners from United Nations or other development agencies, and nominated representatives of civil society and/or networks of people living with HIV (selected on the basis of four criteria: technical knowledge, constituency and regional representation, previous experience with guidelines development). We ensured a balance of representation by region and sex.

All external members of the GDGs and external peer review group completed WHO declaration of interest forms that included participation in consulting and advisory panels, research support and financial investment. There was also a further declaration at the GDG meeting of major roles by members within completed, ongoing or planned clinical trials on either the timing of ART, or evaluation of specific ART regimens. Overall, the WHO secretariat and cochairs of each GDG were satisfied that there had been a transparent declaration of interests, and that no case necessitated exclusion from the discussions.

Four face-to-face GDG meetings were held in Geneva, Switzerland, between November 2012 and January 2013. The decision-making process and formulation of recommendations involved first a critical review of the evidence based mainly on systematic reviews of randomized clinical trials and, where appropriate, observational studies. It also considered of the overall balance of benefits and harms to the individual and at a population level, community values and health worker preferences, resource use, cost-effectiveness, feasibility and constraints to implementation in multiple settings, and issues of equity and human rights.

The GDGs discussed both the proposed wording of the recommendations and the rating of its strength (strong or conditional). All decisions were reached by discussion and consensus on the recommendations, including their strength and, if appropriate, the conditions to be attached to the recommendations. Disagreements were resolved through e-mail discussions, teleconferences and redrafting recommendations and rationale. Early drafts of sections of the guidelines were circulated to GDG members, and a full draft of the guidelines was circulated to GDG members and peer reviewers for comment. A core coordinating group meeting including cochairs of the four GDGs was held in February 2013 to ensure coherence and consistency of recommendations across the guidelines.

Key recommendations: strength of recommendations and quality of evidence

In July 2013, the guidelines were launched at the International AIDS Society conference held in Kuala Lumpur, Malaysia, and subsequently disseminated as a printed and electronic version, including a shorter policy brief in seven languages (Arabic, Chinese, English, French, Portuguese, Russian, Spanish), with an additional web version, that includes user-friendly navigation and all supporting documentation and evidence as annexes.

There were a total of 56 new recommendations in the 2013 WHO 'Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection' [1]: twenty-four were recommendations focused on adults (including pregnant women), and eighteen on children; ten were on service delivery and four on HIV testing. The most important new clinical recommendations were earlier ART initiation, starting ART in all adults with a $CD4^+$ T-cell count of 500 cells/mm^3 or less (but prioritizing those with advanced clinical disease or a $CD4^+$ count less than 350 cells/mm^3); ART initiation regardless of $CD4^+$ cell count in pregnant and breastfeeding women, children under 5 years of age, HIV-infected partners in serodiscordant couples and those coinfected with TB, or severe hepatitis B infection; a preferred first-line ART regimen of TDF + lamivudine or emtricitabine + efavirenz (EVF) as a once-daily fixed-dose combination for adults, pregnant women and children aged 3 years and older; and the use of viral load testing as the preferred approach to monitoring ART response and diagnosing treatment failure. There were four recommendations on expansion of community-level testing, and also ten recommendations on improving the efficiency of HIV services, through decentralizing ART delivery to primary healthcare and community levels, integrating ART services within antenatal, child health and other services, task-shifting to address gaps in health staff capacity; and strategies to improve retention in care, and adherence to ART.

Table 2 summarizes the strength of recommendation and quality of evidence for all recommendations, and then according to population and topic. Forty-five of the 56 recommendations (83%) were ranked as strong, and based respectively on high [two (4.4%)]; moderate [22 (48.9%)]; low [16 (35.6%)] or very low [5 (11.1%)] quality of evidence. The remaining 11 recommendations (19.6%) were conditional, of which 63.6% were based on low and 36.4% on very low quality evidence. Some trends were apparent according to population and topic. All of the fourteen service delivery and HIV testing recommendations were categorized as strong, compared with 79% of the twenty-four adult and 66.7% of the eighteen paediatric recommendations. While all fourteen strong service delivery/testing recommendations were based on low or very low quality evidence, this was 50% for the twelve strong paediatric recommendations, and only 25% of the twenty-four strong recommendations in adults. The weaker evidence base in paediatric HIV care and for service delivery interventions is well recognised, and these were identified as priority areas for operational and implementation research during the guidelines process. More importantly, there are key challenges in ensuring consistent adherence to the GRADE guidance on appropriate rating of recommendations as strong rather than conditional. There is also a need to address a perception and concern among some guideline group members that a conditional recommendation may not be taken seriously and adopted by countries. Where strong recommendations are made based on low quality evidence, it is critical that a clear rationale is provided.

Table 2. Summary of strength of recommendations and rating of quality of evidence of 56 recommendations in 2013 consolidated guidelines.

	Strength of recommendation	
Quality of evidence rating	Strong	Conditional
(a) All recommendations		
High	2 (4.4%)	
Moderate	22 (48.9%)	
Low	16 (35.6%)	7 (63.6%)
Very low	5 (11.1%)	4 (36.4%)
Total	45	11
(b) Adult recommendations	Strong	Conditional
High	2 (10.5%)	
Moderate	11 (57.9%)	
Low	6 (31.6%)	4 (80%)
Very low		1 (20%)
Total	19	5
(c) Paediatric recommendations	Strong	Conditional
High		
Moderate	6 (50%)	
Low	6 (50%)	3 (50%)
Very low		3 (50%)
Total	12	6
(d) Service delivery/HIV testing recommendations	Strong	Conditional
High		
Moderate	5 (35.7%)	
Low	4 (28.6%)	
Very low	5 (35.7%)	
Total	14	

A recent evaluation of 456 recommendations from forty-three different WHO guidelines that had used the GRADE approach also observed that strong recommendations based on low or very low quality evidence were frequently made (55.2% of 290 strong recommendations) [42], so this phenomenon is not specific to HIV care guidelines.

Guidelines dissemination and next steps

Following the release of the guidelines, WHO headquarters and regional offices have worked with national ministries of health and in-country stakeholders to support national evaluation and adaptation through a series of regional dissemination workshops (Yogjakarta, Indonesia; Bejiing, China; Casablanca, Morocco; Pretoria, South Africa; Accra, Ghana; Buenos Aires, Argentina; and Istanbul, Turkey) held between July and November 2013.

The consolidated guidelines will be comprehensively reviewed and updated every two years as new evidence emerges and practice evolves in the use of ART. In addition, there will be regular updates through technical and programmatic supplementary guidance, with one in early 2014 (technical updates on early infant diagnosis, scale-up of viral load monitoring and drug toxicity monitoring) and another in July 2014 (guidance on management of important co-infections, including Cryptococcus, HIV-related oral and skin conditions, hepatitis C, use of cotrimoxazole prophylaxis, linkage and retention in care, and community ART delivery). An Implementation science meeting was held with key partners in February 2014, and involved mapping of key research gaps in the 2013 consolidated guidelines and the research agenda to inform development of future ART-related guidance. WHO will also release consolidated guidelines in 2014 in two other areas: Key populations; and Strategic Information, which will provide a minimum set of quality indicators for HIV prevention and treatment programmes.

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Conflicts of interest

There are no conflicts of interest.

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