Adoption of national recommendations related to use of antiretroviral therapy before and shortly following the launch of the 2013 WHO consolidated guidelines

Lisa J. Nelson, Michael Beusenberg, Vincent Habiyambere, Nathan Shaffer, Marco A. Vitoria, Raul Gonzalez Montero, Philippa J. Easterbrook and Meg C. Doherty

Objective: To determine the status of key national policies on the use of antiretroviral therapy (ART) at the time of the launch of the 2013 WHO consolidated guidelines as well as to track early progress towards adoption of these recommendations following dissemination.

Design: Descriptive analysis of global data on baseline ART policies as of June 2013 and early intentions to adopt the 2013 WHO for use of antiretroviral drugs guidelines as of November 2013.

Methods: Compilation of existing global reports on key HIV policies, review of national guidelines, data collection through annual drug procurement surveys and through guidelines dissemination meetings in each of the six WHO regions.

Results: Data were available from 124 low- and middle-income countries, including 97% of the 57 high-priority countries that have been identified by WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS). At baseline, only one country reported recommending antiretroviral therapy (ART) at a CD4+ T-cell count 250 cells/µl or less for adults and adolescents in 2013, whereas nine countries already recommended using CD4+ T-cell count 500 cells/µl or less. Recommendations for ART initiation regardless of CD4+ T-cell count for HIV-infected patients with tuberculosis (86%), hepatitis B (75%), all HIV-infected women who were pregnant or breastfeeding (option B+40%) or HIV-infected persons in a serodiscordant relationship (26%) had been nationally adopted as of June 2013. Eight of 67 countries (12%) already recommended treating all children less than 5 years of age. The triple antiretroviral combination of tenofovir + lamivudine (or emtricitabine) + efavirenz was recommended as the preferred first-line option for adults and adolescents more frequently (51%) than for pregnant women (38%), or for both adults/adolescents and pregnant women (28%; \( P < 0.05 \)). Fewer than half (37%) of all countries reported recommending lopinavir/ritonavir for all HIV-infected children less than 3 years of age; 54% of countries reported recommending routine viral load monitoring, whereas only 41% recommended nurse-initiated ART.

Conclusions: A number of key WHO policy recommendations on antiretroviral drug use were adopted rapidly by countries in advance of or shortly following the launch of the 2013 guidelines. Efforts are needed to support and track ongoing policy adoption and ensure that it is accompanied by the scale-up of evidence-based interventions.

© 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins

AIDS 2014, 28 (Suppl 2):S217–S224

Keywords: antiretroviral therapy, guidelines, HIV, policies, treatment, WHO
Introduction

On 30 June 2013, the WHO released updated, consolidated guidance on the use of antiretroviral drugs to treat and prevent HIV infection [1]. For the first time, these guidelines brought together recommendations across populations and along a continuum of care in a single consolidated document. These consolidated guidelines built on HIV treatment guidance in support of a public health approach that were first published in 2002 and have been since updated regularly. These new guidelines promote earlier treatment initiation, more effective, less toxic and simpler to use regimens, and improved patient monitoring [2].

WHO HIV treatment guidelines have provided recommendations on when to start antiretroviral therapy (ART), what regimens to use for new patients and those who have failed a first-line regimen, and how to monitor response to treatment for different populations – adults, adolescents, pregnant women, and children. Experience with the adaptation and adoption at national level of previous guidelines has demonstrated that some recommendations were readily adopted, whereas others took far longer to be implemented at a country level despite a solid evidence base in favor of their adoption. For example, although WHO has recommended phasing out stavudine due to cumulative evidence of its long-term toxicities since 2007, some countries still procure this as part of first-line therapy, primarily due to its low cost. Some countries have struggled to update national guidelines in a timely fashion, and not all recommendations are appropriate or adopted in all countries. Following the 2010 WHO ART guidelines, most countries took almost 2 years to adopt the new recommendations.

We assessed national policies at the time of the 2013 WHO antiretroviral drug consolidated guidelines launch (June 2013) and have tracked early intentions for adoption of key HIV treatment policies (as of November 2013) related to when to start ART, what ART regimens to use and how to monitor response to therapy, and key service delivery recommendations across all population groups: adults and adolescents, pregnant women, and children. Table 1 summarizes both 2010 and 2013 recommendations, as most countries prior to the guidelines launch in 2013 were still implementing the recommendations from 2010. Two other key policy documents were released in 2012, one related to the lifelong treatment with ART for all HIV-positive pregnant and breastfeeding women for programmatic reasons (option B+) [3] and the other related to ART initiation for the HIV-infected partner in a serodiscordant relationship irrespective of clinical or immunologic status [6]. These topics were incorporated as formal recommendations into the 2013 consolidated antiretroviral drug guidelines.

The focus of this review was on low and middle-income countries (LMICs) (n = 145) as defined by the World Bank [7], since the 2013 guidelines provide a public health approach to scaling up HIV care and treatment, and these countries are generally the primary focus of global reporting efforts. In addition, WHO and UNAIDS (together with regional staff) have identified 57 high-priority LMICs that generally represent the highest HIV burden. These are listed in Annex 1 (http://links.lww.com/QAD/A494).

Methods

Existing data available at global level reviewed. These included Global AIDS Response Progress Reporting (GARPR) (implemented by WHO, The Joint United Nations Program on HIV/AIDS (UNAIDS), and the United Nations Children’s Fund (UNICEF)), and an annual survey conducted by the WHO HIV Department on antiretroviral drug and diagnostic use in LMICs [8], in addition to regional reports and analyses [9]. Data on antiretroviral drug use and GARPR data from 2013 reflect responses related to policies and implementation in 2012. In addition, these data were augmented with data collected from national HIV program managers, published national guidelines, WHO staff and other stakeholders at regional workshops held in all WHO regions during July to November 2013. Countries were asked to verify current policies (at the time of the launch of the 2013 guidelines, but reflecting WHO recommendations from 2010) and expected key policy changes (when known). In case discrepancies were found in existing data sources, national programs and WHO country staff were contacted to provide and confirm the final data. As the 2013 guidelines contain numerous
Table 1. Key policies evaluated in baseline survey and number of low and middle-income countries responding, 2013.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When to start</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation by CD4⁺ threshold irrespective of clinical status for HIV-infected adults and adolescents</td>
<td>CD4⁺ T-cell count ≤ 350 cells/μl</td>
<td>CD4⁺ T-cell count ≤ 500 cells/μl</td>
<td>92</td>
</tr>
<tr>
<td>ART should be initiated in all individuals with HIV and active TB disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation of ART for all HIV-infected patients with active tuberculosis (TB) disease</td>
<td>ART should be initiated in all individuals with HIV and active TB disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons with HIV-infection and hepatitis B co-infection and chronic active hepatitis</td>
<td>ART should be initiated in all individuals co-infected with HIV and HBV with evidence of severe chronic liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART for women eligible by adult criteria (clinical or CD4⁺ T-cell count ≤ 350 cells/μl; options for prophylaxis: option A (zidovudine + infant nevirapine), option B (triple antiretroviral medication according to national guidelines)</td>
<td>Option B/B+ [3]: All pregnant and breastfeeding women with HIV should initiate triple antiretroviral medication (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No recommendation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Offer ART to all partners with HIV in serodiscordant couples to reduce HIV transmission to uninfected partners (2012 recommendation) [6]</td>
<td></td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>ART should be initiated in all children infected with HIV below 2 years of age irrespective of clinical or immunological status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes phase in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load is recommended as the preferred monitoring approach to diagnose and confirm antiretroviral treatment failure. If viral load is not routinely available, CD4⁺ T-cell count and clinical monitoring should be used to diagnose treatment failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six options and fixed-dose combinations (FDCs) recommended; zidovudine or tenofovir preferred equally, nevirapine and efavirenz both listed as options, phase out of stavudine encouraged</td>
<td>Tenoforv + (lamivudine or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART</td>
<td></td>
<td>97</td>
</tr>
<tr>
<td>ART for women meeting eligibility criteria; for prevention of mother-to-child transmission: option A (zidovudine + infant nevirapine); option B (triple antiretroviral medications)</td>
<td>Tenoforv + (lamivudine or emtricitabine) + efavirenz as a fixed-dose combination is recommended as the preferred option to initiate ART</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td>For children less than 24 months not exposed to antiretroviral medications (or with unknown exposure), start ART with nevirapine + 2 NRTIs; for infants exposed to maternal or infant nevirapine or other NNRTIs used for maternal treatment or PMTCT, start ART with lopinavir/ritonavir + 2 NRTIs; for children more than 24 months and less than 3 years of age, start ART with nevirapine + 2 NRTIs</td>
<td>A lopinavir/ritonavir-based regimen should be used as first-line ART for all children infected with HIV younger than 3 years (36 months) of age, regardless of NNRTI exposure. If lopinavir/ritonavir is not feasible, treatment should be initiated with an nevirapine-based regimen</td>
<td></td>
<td>84</td>
</tr>
<tr>
<td>Task shifting for ART provision</td>
<td>No recommendation</td>
<td>Trained nonphysician clinicians, midwives and nurses can initiate first-line ART and maintain ART</td>
<td>65</td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PMTCT, prevention of mother-to-child transmission.
recommendations for different populations and topics, and data on some recommendations are difficult to obtain (particularly for service delivery recommendations), we focused on a number of key parameters with results available at the global level. These are summarized in Table 1 along with response rates from countries where data were available.

**Results**

**Baseline (June 2013)**

Table 2 lists countries participating in the consolidated guidelines dissemination workshops, which were generally high-burden and high-priority countries in each region. In some regions (the Americas), all countries were invited to participate. Overall, 90 (62%) LMIC countries participated in at least one workshop. Among 145 LMICs, data on at least one element were available for 124 (86%) countries. Among the 57 priority countries for WHO and UNAIDS (that were also low or low-middle income status), data were available for 55 (97%).

All regions were well represented, with countries with at least one data element reporting from Africa (87%), the Eastern Mediterranean (100%), Europe and Central Asia (77%), South-east Asia (91%) and the Western Pacific (62%). Figures 1 to 3 show reported national policies as of June 2013, just prior to the launch of the new guidelines.

**When to start and how to monitor**

Among countries reporting on when to start among adults and adolescents as of June 2013 (n = 86), only one country (Afghanistan) recommended a CD4+ T-cell count threshold for ART initiation below 250 cells/μl. At the time of the guidelines launch, 9 (7%) countries in the Americas (Argentina, Belize, Bolivia, Brazil, Costa Rica, Ecuador, and Honduras) and elsewhere ( Fiji and Georgia) already recommended using a higher threshold of CD4+ T-cell count of 500 cells/μl or less for ART initiation.

Antiretroviral therapy initiation irrespective of CD4+ T-cell count eligibility criteria for active tuberculosis (TB) was first recommended in 2010, and response rates and uptake were found to be quite high (86% for TB co-infection). Antiretroviral therapy for the HIV-infected partner in a serodiscordant partnership, first recommended in 2012, was adopted by 26% of countries by June 2013.

In 2012, WHO released a programmatic update related to a new model of offering ART to all pregnant women beginning in pregnancy and continuing for life, commonly referred to as ‘option B+’ [3]. Worldwide, of the 112 LMICs with data, 45 (40%) had already adopted option B+ as of June 2013. Uptake of this recommendation has been similar to the global average in Africa, where 38% of countries have adopted option B+.

(75)Only 67 countries provided data on ART initiation for children regardless of clinical or immunologic status as of June 2013. Among these, eight (12%) (Bolivia, Guatemala, Kyrgyzstan, Mozambique, Rwanda, South Africa and Timor Leste) had already adopted a policy to treat all children less than 5 years of age or all children less than 15 years (Russian Federation). A fifth of countries reporting [14/67 (21%)] continued to recommend treatment irrespective of clinical or immunologic status only for children less than 1 year of age (Angola, Armenia, Azerbaijan, Belarus, Bulgaria, Ethiopia, Kazakhstan, Lao PDR, Lebanon, Republic of Moldova, Sri Lanka, Tajikistan, Thailand, and Yemen), whereas the remaining countries recommended treatment for all children less than 2 years of age.

Table 2. Country participation in WHO dissemination workshops, 2013.

<table>
<thead>
<tr>
<th>Region</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>West and central Africa (November 11–13): Burundi, Cameroon, Chad, Congo, Cote d’Ivoire, Democratic Republic of Congo, Ethiopia, Ghana, Liberia, Nigeria, Sierra Leone, South Sudan, Togo</td>
</tr>
<tr>
<td>European Region (EURO)</td>
<td>Eastern Europe October 29–31: Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Turkmenistan, Tajikistan, Ukraine, Uzbekistan</td>
</tr>
<tr>
<td></td>
<td>September 11–13: Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Sudan, South Sudan, Somalia, United Arab Emirates, Yemen</td>
</tr>
<tr>
<td>Eastern Mediterranean Region (EMRO):</td>
<td></td>
</tr>
<tr>
<td>Region of the Americas (AMRO)</td>
<td>Latin America and Caribbean August 26–28: Chile, Argentina, Uruguay, Brazil, Bolivia, Peru, Ecuador, Colombia, Venezuela, Panama, Costa Rica, Nicaragua, El Salvador, Guatemala, Mexico, Dominican Republic, Belize, Haiti and Cuba, Caribbean: (October 21-23): Antigua/Barbuda, The Bahamas, Belize, Dominica, Grenada, Guyana, Jamaica, Montserrat, St. Kitts/Nevis, St. Lucia, St. Vincent and the Grenadines, Suriname, Trinidad and Tobago</td>
</tr>
<tr>
<td>Western Pacific Region (WPRO)/Southeast Asia Region (SEARO):</td>
<td>Asia July 23–25 and September 16–18: Bangladesh, Bhutan, China, Cambodia, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, Timor Leste</td>
</tr>
</tbody>
</table>

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.
National adoption of 2013 WHO consolidated guidelines Nelson et al.

Fig. 1. National policies in low and middle-income countries for initiating ART in adults and adolescents irrespective of clinical or immunologic status, June 2013.

Fig. 2. National treatment policies for initiating ART in children in low and middle-income countries irrespective of clinical or immunologic status, June 2013.
Since 2010, WHO also recommended the use of viral load monitoring to assess response to ART. Countries may recommend viral load testing for patients with suspected treatment failure (‘targeted virologic monitoring’) or for all patients on a periodic basis (‘routine virological monitoring’). Many countries recommend routine viral load monitoring, but there are significant differences in regional uptake of this recommendation. Among only 69 countries with reported data, 37 (54%) reported they had adopted a routine policy of viral load monitoring in patients and 28 (40%) recommended targeted monitoring (i.e. in those with clinical and immunologic criteria suggestive of treatment failure). A total of 4 (6%) countries reported that viral load was not available in country or there was no clear policy on viral load monitoring.

What to start

By June 2013, 51% of countries had tenofovir + lamivudine (or emtricitabine) + efavirenz as the preferred first-line regimen for HIV-infected adults and adolescents, whereas 39% of countries recommended this same regimen for HIV-infected pregnant and breastfeeding women who either were eligible for treatment or received option B or option B+ for prevention of mother-to-child HIV transmission (PMTCT). Among countries which reported first-line data for both populations, 28% recommended this regimen for both adults/adolescents and pregnant women. However, data from a recent WHO survey (which included data from 59 countries) found a large number of first-line regimens being reported [8]. A total of 66 different options for adult first-line ART were included, among which there were more than five tenofovir-based regimens.

Only 84 countries reported on whether lopinavir/ritonavir was recommended for all HIV-infected children less than 3 years of age, irrespective of exposure to non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as through exposure to PMTCT interventions. Of these, 33 (39%) reported recommending lopinavir/ritonavir for all children less than 3 years of age with HIV infection.

Programmatic and service delivery recommendations

WHO endorsed the adoption of nurse-initiated and nurse-maintained ART based on a systematic review of published evidence in the 2013 recommendations. A total of 27/65 (42%) countries already have policies that allow nurse initiation for at least some population groups. Only Bhutan (where this policy exists but is not practiced), Fiji (for nonpregnant adults), Nepal (for pregnant women), Papua New Guinea, and the Syrian Arab Republic reported having already adopted this policy outside the African region.
Trends in intended adoption of key recommendations (November 2013)

At the time of the last WHO guidelines dissemination workshop (November 2013), when final data were collected at least 68 countries were planning to adopt treatment initiation for all adults and adolescents with a CD4\(^+\) T-cell count \(\leq 500\) cells/\(\mu l\) or less, irrespective of clinical status, and at least 30 had plans to adopt a policy of treating all children less than 5 years of age, including several countries (Ethiopia, Namibia, Russian Federation, and Zambia) which plan to treat all children less than 15 years of age. Some countries plan to adopt these recommendations over the next few years, in part due to the financial resources that will be required to cover more patients on ART. The majority of LMICs surveyed are planning to phase in the recommended first-line regimen for all adults, adolescents, and pregnant and breastfeeding women (51%), but likewise will phase this in as stocks of existing medicines begin to run low. Countries are moving towards a simplified formulary and to the procurement of fixed-dose combinations (FDCs) when these are available. Many countries report that they will expand the routine use of viral load to monitor patient response to ART in a phased manner. However, despite new evidence-based recommendations for nurse and nonphysician-initiated ART, there appears to be little movement to adopt this recommendation in countries and regions that have not already done so. Some countries face legal and cultural barriers, and not all regions see this recommendation as relevant for their context. Figure 4 compares national adoption of policies at baseline (June 2013) compared with intended adoption as of November 2013.

Discussion

It has now been over a decade since countries began large-scale national programs to treat people living with HIV (PLHIV) following guidelines from WHO. Countries therefore have substantial experience with reviewing and adapting guidelines at national level. By 2013, uptake of the guidance from 2010 to 2012 on ART for HIV-serodiscordant couples and a programmatic update related to option B+ had been adopted by 26 and 40% of LMICs, respectively. Early indications are that adaptation discussions in most countries are well advanced, and Ministries of Health plan to adopt policies for earlier ART initiation for HIV-infected adults and adolescents (to a CD4\(^+\) T-cell count \(\leq 500\) cells/\(\mu l\)), pregnant women, children below 5 years, and for other situations regardless of CD4\(^+\) T-cell count, such as active TB, severe chronic hepatitis B, and HIV-serodiscordant couples. This analysis complements a recent evaluation by Gupta and Granich [11], which evaluated ART initiation criteria in adults and pregnant women, but did not examine policies related to children, recommended regimens, or use of viral load monitoring. A comparison with that analysis reveals very significant scale-up of the recommendation to treat all HIV-infected TB patients (from 33 to 86%), for option B+ (from 14 to 40%) and ART for HIV-serodiscordant couples (from 3 to

![Fig. 4. Comparison of reported policies at baseline (June 2013) compared with intended adoption (November 2013) among low and middle-income countries.](https://example.com/fig4.jpg)
24 countries) over a short period of time. Despite differences in methodology and countries included in the analysis, the trends are clear.

Although many countries already recommend a TDF-containing regimen (especially for nonpregnant adults and adolescents), this is frequently one of a range of first-line options and not always available as a FDC tablet. As countries aim for further scale-up of treatment services to more decentralized sites, it is imperative that the supply chain for first-line regimens is simplified as much as possible. Supplies of key lab-related commodities for HIV testing (including virological HIV diagnosis of infants) and monitoring (through viral load and CD4 T-cell count testing) must also be simplified and streamlined if they are to be taken to scale. The high number of regimens used increases market fragmentation and inefficiency in procurement, losing the opportunity for an economy of scale. Drug optimization, recommending one preferred once-daily FDC regimen for first-line ART for HIV-infected adults and adolescents and for children when available should be promoted.

**Limitations**

The analysis focused only on policy recommendations and so did not evaluate the level of coverage or implementation of recommendations, which are critical issues. It is evident that some policies (such as the use of viral load monitoring or lopinavir/ritonavir for HIV-infected children) have been widely adopted but their coverage remains low in many high-burden countries. In general, data on adult/adolescent ART initiation criteria and regimens used were more readily available than data for children, especially as many countries procure numerous regimens for children of different ages, making such data difficult to obtain and track. Key service delivery recommendations, provided for the first time in 2013, were also difficult to track, as policies related to task-shifting such as nurse-initiated ART or integration of care services are not always available in national guidelines or global reporting mechanisms. Future revisions to global reporting should aim to capture these key policy domains.

In conclusion, WHO plays a lead role in the development of evidence-based policies at the global level, but this must be followed by regional and country-level discussions. Global and national policies are necessary but not sufficient to scale up key antiretroviral drug-based HIV treatment and care services. Antiretroviral drug-based strategies also provide a key prevention benefit, and complement other prevention strategies. WHO expects to revise the 2013 guidelines in 2015. Lessons learned from the uptake and the dissemination of the 2013 guidelines will permit improvements to future guidelines processes.

**Acknowledgements**

The authors are grateful to Theresa Babovic, Cadi Irvine, Michelle Williams, Mayada Youssef Fox, and regional/country WHO staff (Monica Alonso–Gonzalez, Emil Asamoah–Odei, Françoise Bigirimana, Agnes Chetty, Isseu Diop Touré, Nerisse Dominguez, Martin Donoghoe, Irina Eramova, Massimo Ghidinelli, Masaya Kato, Dinnyu Kombate–Noudjo, Zhang Lan, Ying-Ru Lo, Frank Lule, Amaya Maw–Naing, Razia Pendse, Dominique Ricard, Gabriele Riedner, Nicole Seguy, and Dongbao Yu) who assisted with data completion and review. We are grateful to Florence Rusciano for assistance in producing the maps.

**Conflicts of interest**

Source of funding: None.

**References**

8. World Health Organization. AMDS survey on ARV use and laboratory use and implementation of WHO-related guidelines. 2013.