

# The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings

Charles F Gilks, Siobhan Crowley, René Ekpin, Sandy Gove, Jos Perriens, Yves Souteyrand, Don Sutherland, Marco Vitoria, Teguest Guerma, Kevin De Cock

WHO has proposed a public-health approach to antiretroviral therapy (ART) to enable scaling-up access to treatment for HIV-positive people in developing countries, recognising that the western model of specialist physician management and advanced laboratory monitoring is not feasible in resource-poor settings. In this approach, standardised simplified treatment protocols and decentralised service delivery enable treatment to be delivered to large numbers of HIV-positive adults and children through the public and private sector. Simplified tools and approaches to clinical decision-making, centred on the “four Ss”—when to: start drug treatment; substitute for toxicity; switch after treatment failure; and stop—enable lower level health-care workers to deliver care. Simple limited formularies have driven large-scale production of fixed-dose combinations for first-line treatment for adults and lowered prices, but to ensure access to ART in the poorest countries, the care and drugs should be given free at point of service delivery. Population-based surveillance for acquired and transmitted resistance is needed to address concerns that switching regimens on the basis of clinical criteria for failure alone could lead to widespread emergence of drug-resistant virus strains. The integrated management of adult or childhood illness (IMAI/IMCI) facilitates decentralised implementation that is integrated within existing health systems. Simplified operational guidelines, tools, and training materials enable clinical teams in primary-care and second-level facilities to deliver HIV prevention, HIV care, and ART, and to use a standardised patient-tracking system.

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Department of HIV/AIDS,  
World Health Organization,  
Geneva 1211, Switzerland  
(Prof C F Gilks FRCP,  
S Crowley MRCP,  
René Ekpin MD, S Gove MD;  
Jos Perriens MD,  
Y Souteyrand PhD,  
D Sutherland MD, M Vitoria MD,  
T Guerma MD, K De Cock FRCP)

Correspondence to:  
Prof Charles Gilks  
gilks@who.int

## Background

Around 40 million people worldwide are thought to be infected with HIV. Many of these people live in developing countries. Since 2001, the WHO has been promoting a public-health approach to antiretroviral therapy (ART) to improve access in resource-poor settings. Existing guidelines for ART,<sup>1,2</sup> and the prevention of mother-to-child transmission<sup>3</sup> were revised earlier this year, and separate guidelines for treating children were developed.<sup>4–6</sup> Other publications support the public-health approach to ART delivery<sup>7–9</sup> and free<sup>10</sup> and equitable access<sup>11</sup> to ART. The integrated management of adult, adolescent, and childhood illness (IMAI/IMCI) has been developed to support decentralised implementation in resource-poor countries.<sup>12</sup>

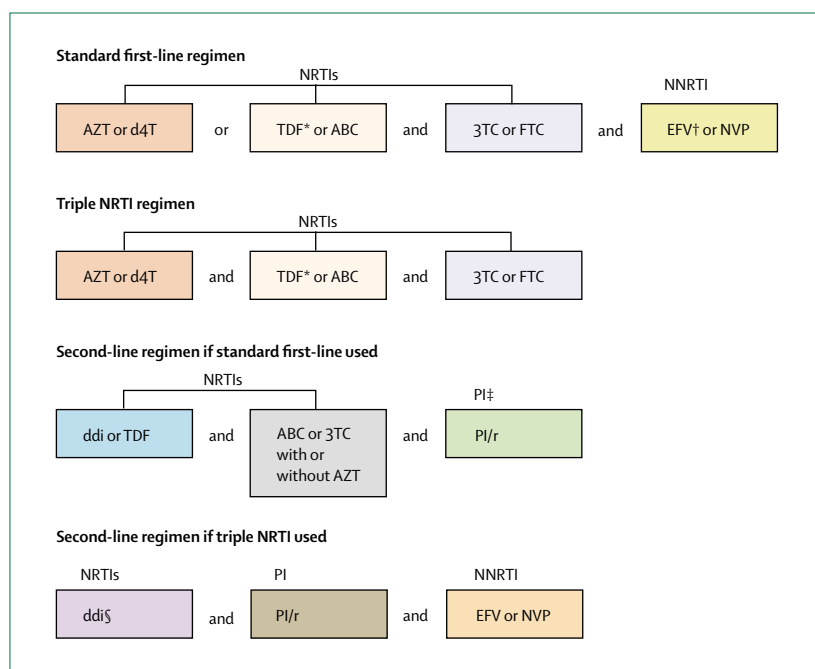
Treatment options have been consolidated into two sequential ART regimens.<sup>2</sup> International consensus on a simple first-line antiretroviral combination for adults meant that production and supply of ARTs could be scaled-up. Once fixed-dose combinations became widely available, and prices had fallen substantially, the WHO announced its 3 by 5 initiative (to strive for 3 million people in low-income and middle-income countries to be on antiretrovirals by 2005).<sup>13</sup> Although the initiative did not meet its target, by the end of 2005, around 1·3 million people were receiving WHO-recommended first-line regimens,<sup>14</sup> compared with 400 000 in 2003. A recent assessment noted that almost all focus countries for ART scale-up had either adapted or used WHO recommendations to shape national policy;<sup>15</sup> treatment programmes and centres report good initial responses.<sup>16,17</sup> Despite these achievements, there remains considerable uncertainty about what should constitute a public-health approach to ART. We summarise here the WHO's

approach, and clarify its importance for treatment providers, HIV programme managers, and policymakers in developing countries.

## Why a public-health approach?

Extensive evidence shows that combined antiretrovirals can substantially extend the life of those with HIV/AIDS. Guidelines for industrialised countries cover individual patient management delivered by specialist doctors prescribing from the full range of antiretrovirals, supported by routine high-technology laboratory monitoring.<sup>18,19</sup> Such an approach is not feasible in resource-limited settings where doctors are scarce (eg, one per 12 500 population in Uganda<sup>20</sup>), laboratory infrastructure is inadequate (eg, one working microscope per 100 000 population in central Malawi<sup>21</sup>), and the procurement and supply-chain management is fragile. This difficulty in translating guidelines from developed to developing nations caused concerns over whether ART scale-up in poor countries was feasible, let alone affordable or cost-effective.

Drawing on experience from using the DOTS approach for tuberculosis, the WHO began to develop a public-health approach to providing ART. This approach took into account country requirements, the realities of weak health systems, and the experiences of pioneering ART programmes.<sup>22</sup> The key tenets were standardisation and simplification of regimens to support efficient implementation, ensuring ART programmes were based on the most rigorous scientific data,<sup>1</sup> and equity—aiming to set standards for treatment that should be accessible by all in need. The key conceptual shift was the move from an individual-based approach to a population-based one, recognised as the only way to make ART rapidly accessible to the millions in need.<sup>23</sup>



**Figure: Recommended first and second-line ART regimens**

AZT=zidovudine. d4T=stavudine. 3TC=lamivudine. FTC=emtricitabine. TDF=tenofovir. ABC=abacavir. EFV=efavirenz. NVP=nevirapine. \*Not used for children younger than 13 years. †Not recommended for children younger than 3 years or weighing less than 10 kg. ‡PI choices are more limited in children. §Optional. The triple NRTI approach can be used to avoid NNRTI drug-drug interactions and toxicity. AZT and 3TC could be used "strategically"; AZT can prevent or delay the emergence of the K65R mutation, and 3TC can maintain the M184V mutation that could reduce the virus' ability to replicate as well as induce some viral resensitisation to AZT.

### Developing a public-health ART approach Standardised regimens and simplified formularies

The first, arguably most important, achievement has been to standardise first-line and second-line treatments. There are three classes of oral antiretrovirals available: nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTI and NNRTI) and protease inhibitors (PI). Public-health therapy readily accommodates the use of two sequential triple-drug ART regimens. On the basis of available data, the initial consensus was to use one NNRTI in first-line treatment, supported by an NRTI;<sup>2</sup> this remains in the 2006 recommendations.<sup>4-6</sup> PIs are reserved for second-line therapy, supported by an NRTI using two new (previously unused) agents to minimise cross-resistance. Second-line potency depends on the PI class, and any initial treatment that includes a PI uses a class preserved for second line therapy, and makes efforts to construct a potent second line regimen impossible.

To derive a simplified antiretroviral formulary and make ART scale-up feasible, it has proven necessary to be prescriptive about first-line and second-line treatment options (figure). Issues of potency, durability of efficacy, ease of administration, tolerability, and toxicity need to be balanced with cost and availability. The simple formulary has encouraged production of fixed-dose first-line combinations, with four two-drug, four three-drug, and four co-packaged products currently

available from at least 23 producers; and helped drive the price of antiretrovirals down by 37–53% between 2003 and 2005.<sup>14</sup>

There is less experience with, and demand for, second-line ART for adults. With limited use and simple formulations not yet developed, the market has not yet responded in the same way it did for first-line therapy: one fixed-dose combination is produced; prices remain high; and countries are not widely procuring second-line antiretrovirals. Similar constraints have restricted the availability of first-line and second-line treatments for children; only three fixed-dose combinations are available from two manufacturers.

### Simplified clinical decision-making and standardised monitoring

With a standard first-line and second-line sequence of therapy established, patient management can centre on the "four Ss" of simplified clinical decision-making, when to: start; substitute for toxicity; switch treatment after failure; and stop, moving to end-of-life care. This is supported by regular clinical assessment: revised guidelines for staging HIV disease describe four stages for both adults and children (paediatric staging was confusingly three-tiered<sup>1</sup>) and are used to identify when to start ART.<sup>8</sup> Previously staging was hierarchical and irreversible; with immune reconstitution and improvement of clinical status, a new concept of staging on therapy (T-staging) to inform when to switch treatment is being developed. Although treatment decisions can be made with clinical information alone, it is better informed with immunological (CD4-cell) monitoring. The WHO has outlined immunological classification of established HIV infection and is now advocating for much wider access to CD4-monitoring technology (table 1 and table 2).

Viral load monitoring, although desirable, is not currently regarded as essential for patient management within a public-health approach. To some extent this is pragmatic because of the procedure's high cost and technical complexity. A more fundamental reason is the utility of viral load measurement. Defining failure of first-line therapy as any detectable or "low" values in asymptomatic or stable patients could precipitate premature switching of ART regimens with potential loss of subsequent years' benefit from a first-line regimen. Such monitoring is informative as to when to switch regimens only if multiple subsequent individually tailored regimens are feasible. When cohort studies can identify threshold levels that define first-line failure; and simpler technology, ideally point-of-care, to monitor viral load can be developed and marketed, such monitoring may have value for a public-health approach. The WHO advocates for wider access to viral-load monitoring in specialist centres for management of complex cases,<sup>4-6</sup> and for virological diagnostic purposes for infants, including using dry blood-spots.<sup>9</sup>

New WHO guidelines for the diagnosis of HIV infection in children younger than 18 months strongly advocate for

wider access to diagnostics for children to facilitate timely access to ART.

### Standardised toxicity and drug-drug interaction management

All antiretrovirals can have large adverse effects, and some are potentially teratogenic; between-drug interactions, particularly with anti-tuberculosis treatment, are problematic. No single regimen can safely be used for all patients and standardising approaches to accommodate toxicity is challenging. With first-line NRTIs, lamivudine (3TC) is always present in the combination used: fortunately it has low toxicity with minimal drug-drug interactions. WHO guidelines, considering the initial need for less laboratory monitoring, used to advocate the use of stavudine (d4T) over zidovudine (AZT) as the companion nucleoside. As a result, stavudine is now widely available in fixed-dose combinations and at a lower cost than zidovudine. However, with growing concern about longer-term toxicity, especially lipodystrophy and metabolic syndromes, industrialised countries no longer recommend stavudine for initial therapy;<sup>18,19</sup> the new guidelines reflect these developments.<sup>4</sup>

The NNRTI class still have problems with toxicity: nevirapine (NVP), cheap and widely available in fixed-dose combinations, is generally used but can cause severe skin reactions, is hepatotoxic (which can be exacerbated by hepatitis B or C co-infection; and life-threatening hepatotoxicity is more common in women with CD4 counts above 250 cells per mm<sup>3</sup>), and is not easily used with rifampicin.<sup>24</sup> Efavirenz (EFZ) is more costly, less widely available, can cause psychosis, and can be teratogenic. Although the guidelines recommend within-class substitution of nevirapine with efavirenz in the face of severe toxicity, or vice versa, experts worry some toxicity may be class-specific rather than agent-specific and that a new class should be used.<sup>18</sup> However, substituting a PI uses a class of ARV drugs usually reserved for second line therapy.

A “simplification strategy” for managing NNRTI toxicity and drug-drug interactions is evolving—using a third NRTI. Although not a within-class substitution, the triple-nucleoside approach has several advantages: co-management of tuberculosis is facilitated; no excess teratogenic risks are recognised; well tolerated in hepatitis co-infection; no risk of use in patients with higher CD4 counts; it deals with potential class-wide NNRTI toxicity; and also preserves the PI class for second-line treatment.

The newer NRTIs (eg, TDF and ABC) are not yet widely available, are costly and have so far been preserved for second-line options. Some triple NRTI combinations have lower virological potency<sup>25</sup> and some induce resistance rapidly.<sup>26</sup> The experience so far of one regimen (AZT/3TC/TDF) is favourable, however,<sup>27</sup> and triple NRTIs are active against HIV-2.

CD4-cell testing unavailable		CD4-cell testing available*
<b>Adults and adolescents</b>		
WHO stages 1 and 2	Do not treat	Treat if CD4-cell count is less than 200 cells per mm <sup>3</sup>
WHO stage 3	Treat	Consider treatment if CD4-cell count falls below 350 cells per mm <sup>3</sup> † and start ART before CD4-cell count drops below 200 cells per mm <sup>3</sup>
WHO stage 4	Treat irrespective of CD-4 cell count	n/a
<b>Infants and children</b>		
WHO stage 1	Do not treat	Treat if at or below age specific threshold shown in table 2
WHO stage 2	Treatment guided by total cell lymphocyte measurement	Treat if at or below age specific threshold shown in table 2
WHO stage 3	Treat all	Treat if <11 months; if ≥12 months, ART initiation may be delayed if CD4 above age-specific thresholds shown in table 2, or with certain clinical conditions‡
WHO stage 4	Treat all	Treat all

\*CD4-cell count should be measured after stabilisation of any intercurrent condition. †ART should be considered for all HIV-infected pregnant women with CD4-cells <350 cells per mm<sup>3</sup>, and is indicated for all pregnant women with stage 3 disease. ‡For children over 12 months with pulmonary or lymph node tuberculosis, oral hairy leukoplakia, lymphoid interstitial pneumonitis, or thrombocytopenia, the CD4-cell count and clinical status should be used to determine the need for and urgency with which to initiate ART.

**Table 1: Recommendations for initiating ART on the basis of immunological and clinical stage**

	Age-specific recommendation to initiate ART*			
	≤11 months	12–35 months	36–59 months	≥5 years adolescents; adults
Percentage T cells CD4+	<25%	<20%	<15%	<15%
CD4-cell count	<1500 cells per mm <sup>3</sup>	<750 cells per mm <sup>3</sup>	<350 cells per mm <sup>3</sup>	<200 cells per mm <sup>3</sup>

Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging. CD4 is preferably measured after stabilisation of acute presenting conditions.\*ART should be initiated by these cut-off levels, regardless of clinical stage; a drop of CD4-cell count below these levels greatly increases the risk of disease progression and mortality. †CD4 is preferred for children aged <5 years.

**Table 2: Age-specific CD4-cell threshold for defining severe immunodeficiency**

### HIV drug-resistance

Because HIV has a high mutation rate, drug resistance frequently emerges with long-term ART use. Switching ART solely on the basis of clinical criteria means patients will have continued ART in the face of emerging HIV resistance and are therefore likely to have developed extensive mutations associated with antiretroviral drug resistance. One tactic to minimise the emergence of resistance is to provide highly effective first-line regimens, switching to a new class supported by previously unused antiretrovirals. A second is to administer regimens in ways that ensure patients' adherence: fewer pills, simple dosing schedules, and social support for treatment adherence. Good ART programming, with adequate treatment preparation and uninterrupted antiretroviral supplies, is crucial.

WHO has developed a global strategy for monitoring and surveillance of HIV drug-resistance:<sup>28</sup> monitoring the

emergence of resistance in populations on ART at sentinel sites with surveillance for transmission of resistant strains of the virus in recently-infected populations. It is establishing, with partners, a network of assessed and accredited laboratories to undertake resistance testing; monitoring, and surveillance using standard protocols; and analysis and interpretation of early-warning indicators. The appearance and evolution of transmitted drug-resistant variants is one indicator of the effectiveness of efforts at preventing HIV transmission for those on ART. The speed and level at which acquired resistance appears can help identify programmatic components such as clinic accessibility, adherence rates and stock-outs that can be acted upon to delay the emergence of resistant virus. The reported pattern and rates of transmitted and acquired drug-resistant HIV variants will collectively inform regional and global recommendations on which ARVs to maintain or change in first and second-line regimens. WHO does not recommend individual HIV drug resistance testing for individual ART adjustment but uses clinical and other immunological and virological testing, if available, for patient management. Population studies of the emergence of drug resistance at sentinel sites can be used to adjust national ART programme guidelines.

### Implementing a public-health ART approach Decentralised, integrated delivery of care

Population-wide implementation needs simplified and standardised operational approaches. In tandem with the normative work, the WHO has developed and adapted the IMAI/IMCI approach to put into action ART guidelines and evidence-based standards, and provide implementation tools to support decentralisation of ART within integrated HIV services.<sup>12</sup> Increasingly with treatment scale-up, most ART is delivered outside specialist tertiary centres, decentralised to the health district.<sup>17</sup>

IMAI/IMCI provides practical tools for country adaptation, including health-service management at national and district level; training and job-aids for clinical teams; strong follow-up after training, based on clinical and counselling mentors and supportive supervision; materials to support patient education and self-management; and a standard and simple patient-monitoring system, developed with many partners.<sup>28</sup> Provider-initiated HIV-testing and counselling, prevention (for both HIV-uninfected and infected), and prevention of transmission within the health setting are included. These tools support the broad delivery of simplified and standardised services provided through district networks with treatment teams headed by doctors or medical officers but largely composed of nurses, clinical officers, and people living with HIV and other lay providers trained (and paid) to join the clinical team, working with community health workers and community-based organisations. Many countries have

successfully adapted and implemented the IMAI/IMCI materials, and others have started the process of reviewing their scale-up approach and adapting IMAI/IMCI materials to further decentralise and scale-up integrated HIV treatment, care, and prevention.

### Task shifting and specialist support

Where the burden of HIV disease is high, clinical teams at primary-care facilities need to be able to treat non-severe opportunistic infections, manage ART, undertake simplified clinical decision-making, and promote prevention of transmission. In view of the small number of doctors in many developing countries with high prevalence of HIV, most teams will rely on nurses or clinical officers. Task shifting, supported by the IMAI/IMCI approach, promotes sharing of clinical management responsibilities to the lowest relevant cadre and into the community, a vital step for chronic disease management and the shift to long-term treatment and care. The most important task shift is to the patient: sustaining effective chronic HIV care with ART needs substantial patient involvement in managing their own illness, adhering to treatment, responding to side effects, and preventing transmission to others.

When complex clinical problems emerge, IMAI/IMCI prepares primary-care health workers to identify these and consult with supervisors or clinical mentors or refer as appropriate. These clinical mentors themselves need specialist support from centres of excellence. Mentoring for both the doctors and nurse or clinical officer-led teams is an integral component of the IMAI/IMCI approach.

### ART free at the point of delivery

Despite substantial price reductions, ART remains costly meaning that long-term sustainability of public sector programmes is a pressing concern. Some countries impose user fees or institute co-payment mechanisms, particularly at the district or local level, to defray partly the costs of implementing ART programmes. Even with sliding fee scales or full reimbursement, uptake of ART is reduced by user fees; for many poor people, treatment costs will remain an insurmountable, highly inequitable barrier. Charging for services is also associated with worse outcome of ART, probably because end user fees reduce long-term adherence and make it more likely that people will drop-out of programmes.<sup>16</sup> In view of existing evidence and from the perspective of the human right to health, countries are being advised to provide free treatment at the point of service delivery.<sup>10</sup> Nevertheless, balancing the competing priorities of sustainability and equitable access remains a major challenge for national programmes.

### Procurement and supply management

Many countries are experiencing significant delays and bottlenecks with the supply of ARVs and other products needed for ART. Training, better management, and

investment in infrastructure and capacity are needed to improve inefficient services and fragile supply chains. Reducing the number of commodities involved (eg, test kit gloves, drugs, pill boxes, cards patient records, etc), both for procurement and distribution to service delivery points, is crucial. Simplified ART formularies are an important advance, but insufficient evidence exists to pinpoint one optimal first-line regimen (as in tuberculosis treatment); countries are currently choosing drug combinations on the basis of availability and cost. More specificity is needed: by programmes to procure the right proportion of first-line and substitution regimens; and by industry to forecast demand for, and then to produce the appropriate products. Strategically-placed buffer stocks help cope with unforeseen shortages.

### Tracking progress

It has been reasonably straightforward to estimate the numbers starting ART: it will be much more difficult to track the progress of chronic disease treatment with no cure or end-point except loss-to-follow-up or death. Using the example of tuberculosis control programmes, standard registers have been developed, with the potential to link to electronic registers.<sup>29</sup> Group cohort analysis from these registers to determine survival on ART and the proportion remaining on a first-line regimen is an important component of quality management.

Timely transfer of data from records and registers to regional and national monitoring units will be difficult wherever health management information systems are weak. Early supervision for sites is likely to be important.<sup>30</sup> Special support may also be needed for evaluation of data to inform programme roll-out, accountability, and reporting progress. For more detail on specific outcomes, many countries will need to undertake special studies on closely followed-up patient cohorts.

### Evidence for the public-health approach to ART provision

The WHO's public-health approach to providing ART is still being refined. Gaps in knowledge have limited the standardisation of some treatment approaches; others have not yet been adequately assessed. The WHO is to convene an expert meeting to review the evidence and prioritise a research agenda relevant to the public-health approach to ART. Several fundamental questions are already apparent (panel)

### Conclusions

The public-health approach promoted by WHO underpins the successful experiences of several countries in scaling up HIV/AIDS services and is based on the principles of simplification, standardisation, decentralisation, equity, and patient and community participation, and has been pivotal in unlocking the treatment agenda, and starting to close the treatment gap between rich and poor countries. More than a million people in developing

#### Panel: Where next for a public-health approach to ART?

- Does the standard sequence of ART class use (NNRTI/ NRTIs followed by PIs) have most effect on overall survival? Using PIs with NRTIs as first-line treatment could be more durable, outweighing the lower potency of an NNRTI-based second line regimen; alternatively, triple NRTI first-line could have more impact overall with less initial toxicity and reserving two potent new classes for second-line
- When is it most cost-effective to start ART? With universal access there could be billions of dollars' difference in costs between treatment initiated at CD4 threshold of 350 cells per mm<sup>3</sup> or that started when CD4 is close to 200 cells per mm<sup>3</sup>
- How is failure best defined? The clinical correlates of failure are assumed with T-staging to be similar to those for starting therapy. With few immunological correlates and no virological thresholds identified, it is proving difficult to construct clear and simple protocols for switching therapy.
- ART will often be given under the supervision of non-specialist doctors with most clinical decision-making done by nurses. How does ART initiated and managed by clinical officers or nurses compare with physician-led care in terms of individual and population-level outcomes?
- How does ART support and facilitate HIV prevention? There are many ways—both positive and negative—in which treatment could affect prevention of transmission of HIV, but little is understood about this at present

countries are benefiting from simplified and standardised therapy, delivered at district level by trained staff who are fully integrated within existing health systems. Adopting a public-health approach to ART permits a comprehensive method of treating and preventing the transmission of HIV, and is a fundamental requirement if we are to support efforts to strive towards universal access to treatment. Children have been left behind in much of the scale up efforts to date, and the increasing need to treat children emphasises the primary importance of preventing the transmission of the virus from mother to child in the first place.

#### Contributors

All authors have contributed to the development of the public-health approach to antiretroviral therapy. M Vitoria, S Crowley, R Ekpini, J Perriens, K De Cock, T Guerna, and C F Gilks have contributed to adult ART guidelines; S Crowley, S Gove, and C F Gilks to paediatric guidelines; R Ekpini, M Vitoria, S Crowley, and C F Gilks to guidelines for the prevention of mother-to-child transmission; S Crowley, M Vitoria, and C F Gilks to guidelines for clinical staging and immunological classification; M Vitoria, S Crowley, S Gilks, J Perriens, K De Cock, and C F Gilks to co-trimoxazole guidelines; D Sutherland and M Vitoria to HIV drug resistance (development and review editing); Y Souteyrand and T Guerna to free and equitable care (review editing); S Gove (development, adaptation, and implementation) and T Guerna (review of IMAI/IMCI). All authors were involved in the initial planning of the report, subsequent drafts, and the final text. The first draft of the paper was written by C F Gilks.



**Conflict of interest statement**

We declare that we have no conflict of interest.

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