

THE STRATEGIC USE OF ANTIRETROVIRALS

TO HELP END THE HIV EPIDEMIC



World Health
Organization

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Acronyms

3TC	lamivudine
ABC	abacavir
AIDS	Acquired Immunodeficiency Syndrome
API	active pharmaceutical ingredient
ART	antiretroviral therapy
ARV	antiretroviral drugs
ATV	atazanavir
AZT	zidovudine
bPI	boosted protease inhibitor
DRV	darunavir
DSMB	data safety monitoring board
EFV	efavirenz
FDC	fixed-dose combination
FSW	female sex worker
FTC	emtricitabine
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-2	human immunodeficiency virus type 2
HTC	HIV testing and counselling
IDU	injecting drug user
InSTI	integrase strand transfer inhibitor (or integrase inhibitor)
LPV/r	lopinavir/ritonavir
MVC	maraviroc
MSM	men who have sex with men
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OI	opportunistic infections
PEP	post-exposure prophylaxis
PI	protease inhibitor
PITC	provider-initiated testing and counselling
PMTCT	prevention of mother-to-child transmission
PoC	point of care
PrEP	pre-exposure prophylaxis
RAL	raltegravir
RTV	ritonavir
TasP	treatment as prevention
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TRIPS	trade-related aspects of intellectual property rights
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Vaginal and Oral Interventions to Control the Epidemic
VOICE	viral load
WHO	World Health Organization
ZDV	zidovudine

1. Executive Summary

This document is a discussion paper, prepared for the 2012 International AIDS Conference in Washington DC, United States of America. It highlights key issues that confront the global community, policy-makers and national programme planners as they seek to make optimal use of antiretroviral drugs (ARVs) as part of the broader response to HIV. It also discusses how ARVs could contribute to eventually ending the HIV epidemic. The paper does not in itself constitute a World Health Organization (WHO) guidance document, even though it summarizes existing WHO guidelines related to ARV use, highlights progress in the *Treatment 2.0* initiative, and summarizes the next steps in WHO's normative work related to ARV use.

A defining moment has arrived in the global HIV response. A series of scientific breakthroughs, strong political commitment and determined country efforts are combining to make the end of the HIV epidemic a realistic prospect. A global plan to eliminate mother-to-child transmission of HIV and keep mothers alive is being implemented with the support of world leaders. In 2011, at the United Nations General Assembly, countries reaffirmed their commitment to achieving "Universal Access" to HIV prevention, treatment, care and support by 2015. Meanwhile, scientists have launched a new initiative to find a cure.

Historic opportunities

Safer, more robust and affordable treatment is now available even in the poorest countries. New technologies allow for earlier HIV diagnosis and reliable treatment monitoring in the remotest of areas. Comprehensive HIV prevention and treatment services are available in some of the most challenging settings, and increasingly are reaching the most marginalized and vulnerable populations.

Some of the most significant new developments relate to the use of ARVs for both treating and preventing HIV. We now have evidence, both observational and from randomized control trials, that antiretroviral therapy (ART) not only

saves lives and keeps people healthy; it also prevents new HIV infections.¹ It is also evident that the preventive effects of ART are optimized when it is used in combination with other prevention methods, such as behaviour change, male and female condoms and medical male circumcision (1). There is additional evidence for the efficacy of using ARVs in particular circumstances for pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP). Modelling suggests that the prospect of ending HIV transmission is within the world's grasp (2). The task now is to realize that potential.

Growing treatment needs

Globally, eight million people living with HIV in low- and middle-income countries were accessing ART at the end of 2011. At the same time, an estimated 15 million people needed ART for their own health in low- and middle income countries, based on WHO's 2010 treatment guidelines. This amounted to treatment coverage of 54% (3).

In early 2012 emerging evidence led WHO to issue guidance related to the use of ART as HIV prevention (TasP). WHO currently recommends that people diagnosed with HIV start ART at CD4+ counts of 350 cells/mm³ or lower, and that early initiation of ART (regardless of CD4+ cell counts) also be offered to serodiscordant couples. In addition, a recent programmatic update on options for preventing mother-to-child transmission (PMTCT) of HIV sets out the implications and benefits of early initiation of ART in pregnant women ("Option B+").² WHO is also working with a number of countries to explore the early initiation of ART in certain key populations (such as sex workers, people who inject drugs and men who have sex with men). Adding pregnant women and key populations to the pool of people currently eligible for ART for their own health would take the overall number of people eligible for ART in low- and middle-income countries from 15 million to 23 million.

Recent studies, along with an improved understanding of the chronic inflammation caused by HIV, point to the potential clinical benefits of starting ART at CD4+ count levels above 350 cells/mm³. Some countries have already adapted their national treatment guidelines accordingly. Changing the ART threshold from 350 to 500 cells/mm³ (in addition to including the groups mentioned above regardless of CD4+ levels), would further increase the pool of people eligible for ART to 25 million.

In the wake of recent research findings and modelling exercises, some have called for a "test-and-treat" approach. This would involve regularly screening entire populations for HIV and initiating immediate treatment for everyone found to be HIV-positive. Such a scenario would increase eligibility for ART to the total 32 million people living with HIV in low-and middle-income countries.

¹ Recent population-based study data show that new HIV infections decrease markedly as ART coverage expands. See Tanser F et al. *Effect of ART coverage on rate of new HIV infections in a hyper-epidemic, rural population: South Africa*. 19th Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, abstract 136LB, 2012.

² "Option B+" entails providing lifelong ART to every pregnant woman diagnosed with HIV, irrespective of her CD4+ cell count.

Difficult choices

As the multiple potential benefits of ARVs become clearer, they are highlighting important technical, operational, programmatic and ethical issues. There are debates about how to balance the benefits and potential risks of earlier initiation of ART, and concerns about the capacities of some countries' health systems to sustain the treatment scale-up. In a context of limited financial resources and persistent health systems constraints, HIV programme managers are confronted with difficult choices among a broadening range of options for using ARVs to reduce HIV morbidity, mortality and transmission. There are also concerns about using ARVs to prevent people from acquiring HIV in a context where almost half the people living with HIV and needing ART are not yet accessing it. This is forcing countries to review their HIV strategies. They need to decide how best to use ARVs for HIV treatment and prevention, and how to combine them with other prevention methods.

New WHO guidance

A key role of WHO is to assess new evidence and experiences, and translate them into global guidance that can inform and guide country decisions. WHO is currently undertaking a systematic review (following the GRADE methodology) to determine whether changes to existing recommendations are warranted. One specific issue is the optimal threshold for treatment initiation, and whether or not to recommend a shift from the current ≤ 350 cells/mm³ to ≤ 500 cells/mm³.

In 2013, WHO will release a revised and consolidated set of guidelines related to the use of ARVs for both HIV treatment and prevention. In particular, it will provide clinical, programmatic and operational guidance to inform countries' implementation approaches and planning decisions¹.

Most low- and middle-income countries are yet to achieve "Universal Access" to ART². There are many reasons for this, starting with the fact that the majority of people do not know their HIV status (4). Large proportions of people who initiate ART only do so once their health is already in serious decline: median CD4+ counts at ART initiation in low- and middle-income countries are currently about 200 cells/mm³. In addition, there is substantial attrition in the "test-treat-retain" continuum. Even in countries with well-developed health systems and high testing rates (such as the United States), less than 30% of people living with HIV are ultimately virally suppressed (5). Strengthening the continuum of care is critically important if the full gains of expanded HIV treatment are to be realized.

¹ The consolidated guidelines will address HIV during the life course (children, adolescents, adults, older adults), include guidance for pregnant women and key affected populations, and address pertinent co-morbidities (such as tuberculosis and viral hepatitis).

² The "Universal Access" target is reached when at least 80% of people in need of ART are receiving in a given country (based on the current WHO recommendation for ART initiation at CD4+ counts of ≤ 350 cells/mm³).

Clearing the obstacles

Other issues need to be addressed as well. Since the start of the expansion of ART in low- and middle-income countries a decade ago, there have been persistent concerns about the emergence of drug resistance. According to a recent report on HIV drug resistance surveillance released at the 2012 International AIDS Conference, drug resistance levels have increased, although not to alarming degrees (6). From 2003 to 2010, antiretroviral use in low- and middle-income countries increased by 22-fold. Drug resistance among people initiating therapy in the areas surveyed stood at 6.8% in 2010. This compares with levels of between 10% and 17% observed in high-income countries. Improved treatment adherence, with improved ART regimens and reliable supplies, will be critical for limiting further spread of drug resistance. Strengthened HIV drug resistance monitoring systems should provide early warning to programme planners, enabling them to select the most appropriate ART regimens.

New technologies and service delivery approaches provide fresh opportunities to overcome some of those difficulties. Rapid HIV tests are available, as are several “point-of-care” technologies for determining CD4+ cell counts, and more technologies for assessing CD4+ cell counts and viral loads are being developed (7). At different levels of health systems, HIV services are increasingly integrated and linked with other health services. Task shifting is being used to deal with growing workloads of people in care, along with outreach services, peer support initiatives and community-based programmes. These innovations all support more timely initiation of ART, and stronger retention in care and treatment adherence. They should be augmented with simplified HIV diagnostic and laboratory processes and further service delivery innovations so that more people are attracted and retained in care. Simpler, less expensive and more robust treatments are also needed, along with more resolute efforts to dismantle social and structural barriers to treatment and care. Close community participation in the design and implementation of treatment programmes is vital.

In order to support and enhance those efforts, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the *Treatment 2.0* initiative in 2011, which promotes innovation and efficiency, and proposes long-term and sustainable strategies (8). As part of that initiative, a global multi-partner platform has been created to develop and implement short- and medium-term priorities to optimize HIV treatment. A similar process is underway in a number of countries that are trying to link forward-looking policies to creative solutions that can simplify and accelerate the scale-up of ART.

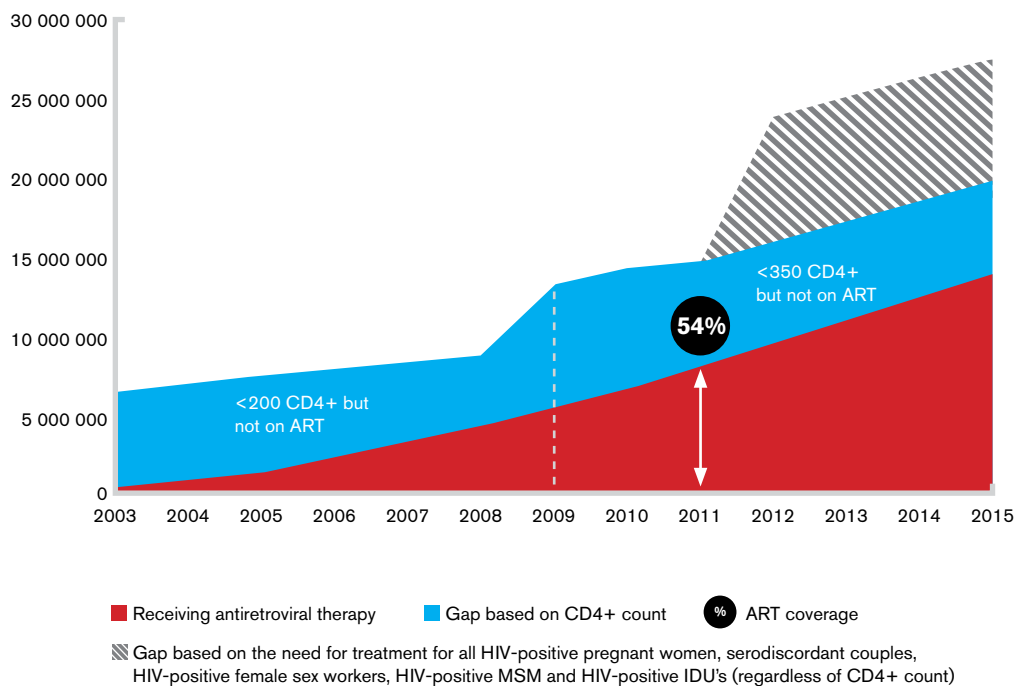
2. Big achievements and huge opportunities

The global expansion of access to HIV treatment ranks among the great recent achievements in public health. At the end of 2011, an estimated 8 million people in low- and middle-income countries were receiving ART – a 25-fold increase since 2002 (3). About 54% of the people eligible for ART for their own health were receiving it at that point (3). Several countries (including resource-limited ones) have reached or are close to achieving “Universal Access” to ART. HIV incidence and mortality rates are falling in many countries (4). Globally, AIDS-related deaths decreased to 1.7 million in 2011, compared with the peak of 2.3 million in 2005 (3). An estimated 2.2 million [2.0–2.4 million] adults were newly infected with HIV in 2011, 500 000 fewer than in 2001 (3).

More people are getting HIV treatment, but the median CD4+ cell count of people starting ART is still well below the current, recommended eligibility threshold for ART initiation. Access to ART is also not yet equitable. The 28% ART coverage for children (younger than 15 years) in need of treatment in 2011 was considerably lower than the 57% coverage for adults (3). Providing ART to pregnant HIV-positive women reduces the risk of HIV transmission to their unborn children to less than 5% and may reduce the risk of transmission to their seronegative partners by 96%. However, less than one third of the women eligible for ART for their own health in 2011 were receiving it (3). Treatment access is also much too low in settings where the epidemic is concentrated among marginalized populations such as sex workers, people who inject drugs, men who have sex with men, and transgender women.

The ART gap (based on a CD4+ threshold of ≤ 350 cells/mm³) has been narrowing considerably, but it still remains wide, as Fig. 1 shows. Nevertheless, the target of having 15 million people on ART in 2015 is achievable. Reaching this goal, set by the United Nations General Assembly in its 2011 Political *Declaration on HIV/AIDS* (9), will require special efforts and innovation. At the same time, as more people become infected with HIV and as ART eligibility criteria change more people will be offered ART.

Figure 1:
ART coverage in low- and middle-income countries



Note: These data reflect the number of people eligible for HIV treatment and prevention using ART, based on WHO guidelines and technical updates. The solid areas represent those eligible for HIV treatment based on CD4+ thresholds. The shaded area represents additional people eligible for treatment based on co-morbidities (TB and chronic active hepatitis), pregnant women and those eligible for ART primarily as HIV prevention (discordant couples and key populations). The 2009 jump in ART gap represents a change in ART eligibility from CD4+ count of ≤ 200 cells/mm³ to ≤ 350 cells/mm³. Although the treatment gap is narrowing, greater progress is needed if the world is to reach the "Universal Access" goal. This is because the number of people needing ART increases due to the natural evolution of the HIV epidemic and because of changing ART eligibility criteria, including shifts towards earlier treatment.

FSW, female sex workers; HIV, Human immunodeficiency Virus; IDU, injecting drug user; MSM, men who have sex with men; TB, tuberculosis.

2.1 NEW OPPORTUNITIES

Recent evidence of the clinical and prevention benefits of ARVs herald major new opportunities for the global HIV response. ARVs are highly effective and vital components of all national HIV responses. Their efficacy for treating HIV and for PMTCT is well established, as is their use as PEP for HIV infection (mainly in cases of occupational exposure and sexual assault). The remarkable efficacy of ARVs for *preventing* sexual transmission and acquisition of HIV has now also been proven.

Table 1:

The effectiveness of various HIV prevention interventions*

* Pooled analysis of data from observational studies on use of opioid substitution therapy and clean injecting equipment and paraphernalia were not included due to heterogeneity of studies.

Study	Population	Study type	Effect size, (95% CI)
Treatment as prevention for HIV-positive women and men in discordant couples			
HPTN 052 (10)	Serodiscordant couples	RCT	96 (82-99)
Anglemyer et al (11)	Serodiscordant couples	Systematic review of 5 studies	84 (on ART RR 0.16 [0.07-0.56])
Attia et al (12)	Serodiscordant couples	Systematic review of 11 cohorts	54 (on ART RR 0.46 [0.19-1.13])
		Sub-analysis of 2 cohorts with VL	100 (on ART with VL less than 400 copies/ml)
Antiretroviral pre-exposure prophylaxis for HIV-negative women and men			
PrEP (13)	Serodiscordant couples	RCT	75 (55-87) for TDF/FTC 67 (44-81) for TDF
TDF2 (14)	Heterosexual men and women	RCT	63 (22-83) for TDF/FTC
iPrEX (15)	MSM	RCT	42 (18-60) for TDF/FTC
CAPRISA 004 (16)	HIV negative women	RCT	39 (6-60)
FEM-PrEP (17)	Women	RCT	DSMB stopped trial for futility
VOICE (18)	Women	RCT	DSMB stopped daily oral TDF arm and daily vaginal gel arm in 2011 for lack of efficacy
Medical male circumcision of HIV-negative men in sub-Saharan Africa			
ANRS 1265 (19)	HIV negative men	RCT	60 (32-76)
Wawer at al (20)	HIV negative men	RCT	55 (22-75)
Bailey et al (21)	HIV negative men	RCT	60 (22-75)
HIV vaccine in Thailand			
Prime-boost HIV Vaccine (Thai RV144) (22)	Thai community	RCT	31 (1-51)
Male condom use			
Weller (23)	Serodiscordant couples	13 cohorts	80 (35.4 - 94.2)

CI, confidence interval; DSMB, data and safety monitoring board; FTC, Emtricitabine; HIV, human immunodeficiency virus; MSM, men who have sex with men; RCT, randomized controlled trial; RR, relative risk; TDF, Tenofovir disoproxil fumarate; VL, viral load; VOICE, Vaginal and Oral Interventions to Control the Epidemic

The most dramatic recent findings came from the HPTN 052 trial¹, which demonstrated that providing immediate ART to the HIV-positive partner² reduced HIV transmission by 96% among serodiscordant couples (10). More recent evidence has shown the preventive effect of ART in “real-life” settings. New analysis from a South African study demonstrates that when treatment uptake is high (i.e. more than 30% of people are receiving it), people not yet infected with HIV are 40% less likely to acquire HIV. For every 10% increase in the share of people getting ART in the study, HIV incidence decreased by 17% (24).

Research is also leading to a better understanding of the chronic inflammation and harm caused by uncontrolled HIV viraemia at all CD4+ levels (25) – findings that favour earlier initiation of ART, even above a CD4+ cell count threshold of 350. A number of studies have also reported an association between CD4+ cell counts and certain non-AIDS complications.³ One large observational cohort study has found associations between earlier ART initiation at CD4+ ≥ 350 cells/mm³ and reduced risk of death, as well as increases in AIDS-free survival rates (26).

However, those benefits have not been consistently observed (27,28,29). A recent, WHO-led meta-analysis, which reviewed observational studies from low- and middle-income countries, found that ART decreased the risk of tuberculosis (TB) by up to 65%, irrespective of CD4+ cell count (30). Analyses from the HPTN 052 trial have found a significant reduction in HIV-related clinical events for patients who started ART at CD4+ cell counts below 550mm³ (10).

Other controlled randomized trials that are specifically designed to assess the benefit of early ART initiation are expected to conclude in the coming three years (31,32). WHO has begun a systematic review of evidence for the clinical benefits of ART initiation above CD4+ cell counts of 350/mm³, which will inform a possible future recommendation on the optimal ART eligibility threshold.

Recent research findings have led WHO to recommend that ART be offered to the HIV-infected partner in serodiscordant couples regardless of CD4+ cell count in order to prevent HIV transmission to the uninfected partner.


¹ The trial was conducted in Botswana, Brazil, India, Malawi, South Africa, Thailand and Zimbabwe.

² With a CD4+ count between 350 and 550 cells/mm³.


³ These include malignancies and renal problems, cardiovascular disease, liver disease, neuropsychological decline and HIV-associated neurocognitive disorders, and increased risk of fracture. Inflammatory markers have been associated with mortality and cardiovascular events, although the role of chronic inflammation in disease progression remains unclear.

Recent studies have provided mixed findings on the efficacy of specific oral (tenofovir-based) PrEP regimens for preventing uninfected people from acquiring HIV (see Table 1).¹ To date, the efficacy of topical ARV-based products for PrEP has been established in only one trial (CAPRISA 004) (16). The available evidence suggests the possibility of using PrEP for specific prevention “niches” (such as in discordant couples where the HIV-positive partner is not on ART, and for men who have sex with men and are at high risk of being exposed to HIV). The issue of adherence, however, is likely to be a major challenge when implementing PrEP at population level, as has been seen even in controlled trial settings.

Given the increasing range of treatment and prevention options, and growing resource constraints, difficult decisions need to be made. Using ARVs most strategically requires careful decision-making at the clinical, operational and programmatic levels. Strong evidence, good practice and solid ethical and equity principles should guide those decisions.



Further investigation is required to clarify the potential role of PrEP in combination HIV prevention strategies, and to determine how PrEP may be delivered at scale.

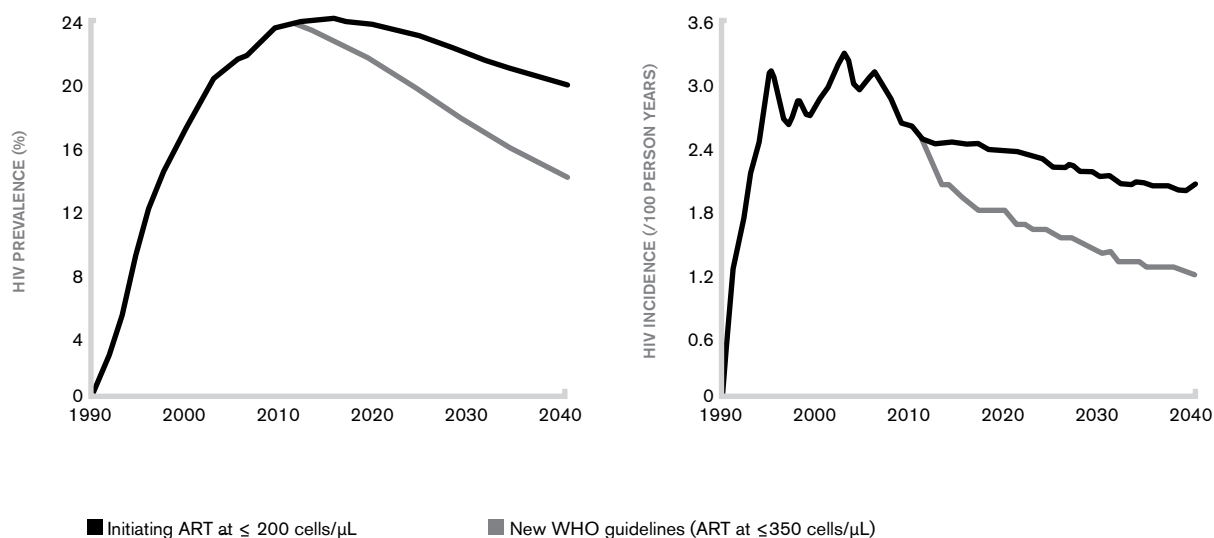


¹ Efficacy has been demonstrated in serodiscordant couples, men who have sex with men, and young women and men.

2.2 LOOKING AHEAD

Increased treatment access is very likely to be contributing to the gradual decline in global HIV incidence – as suggested in Fig. 2, which is based on study data from South Africa, and which depicts the projected impact of earlier ART initiation on HIV trends.

Figure 2:
Projected impact of ART at CD4+ cell counts of ≤ 200 ml/mm³ and at ≤ 350 ml/mm³ on HIV prevalence and incidence in the Hlabisa sub-district, South Africa, 1990-2040



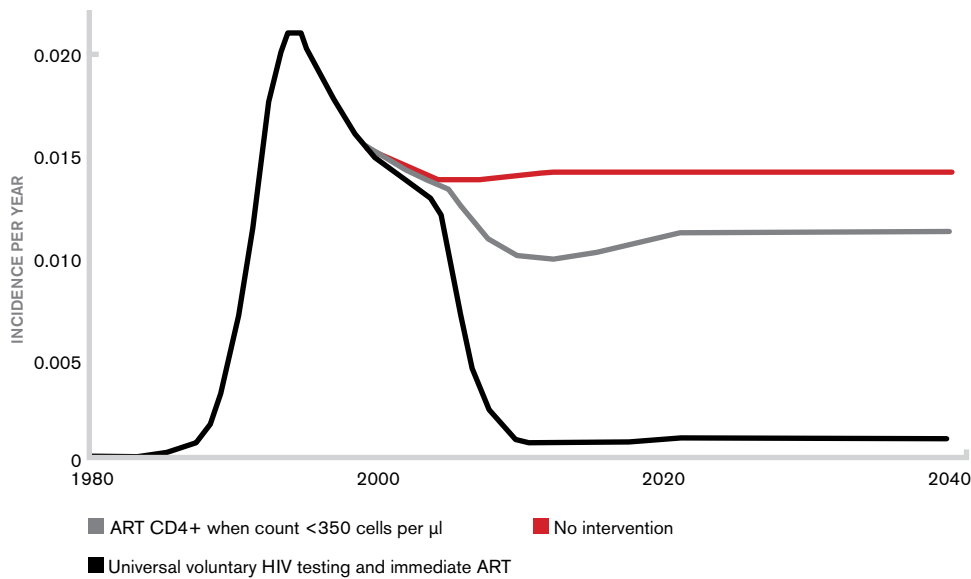
ART, antiretroviral therapy; HIV, human immunodeficiency virus; WHO, World Health Organization.

Source: Hontelez JAC, de Vlas SJ, Tanser F, Bakker R, Barnighausen T et al. The Impact of the New WHO Antiretroviral Treatment Guidelines on HIV Epidemic Dynamics and Cost in South Africa. *PLoS ONE*, 2011; 6(7):e21919.

ART, antiretroviral therapy; HIV, human immunodeficiency virus;

Recent modelling efforts have explored various possibilities for scaling up ART and HIV testing and counselling (HTC), and other interventions. A WHO model published in the *Lancet* in 2008, and based on somewhat optimistic assumptions, suggested that annual HIV testing of all adults, coupled with immediate ART and high adherence rates, could result in the elimination of HIV within 10 years in a setting with a generalized epidemic and high HIV prevalence, such as South Africa (see Fig. 3). Several other models, using different parameters, have arrived at directionally similar conclusions (34).

Figure 3:
Model projections illustrating the potential impact on HIV incidence in South Africa of annual voluntary HIV testing and counselling and ART



ART, antiretroviral therapy; HIV, human immunodeficiency virus.

Source: Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* 2009;373(9657):48-57.

Models that have explored a combination of various prevention strategies confirm the super-additive effects of using prevention strategies in such a manner (35). “Combination prevention” encompasses non-ARV based interventions (including biomedical, behavioural and/or structural ones) plus the use of ARVs, primarily through the early initiation of ART. That includes using ART to prevent HIV transmission and, for certain individuals and in particular circumstances, using ARVs for PrEP and PEP to prevent HIV acquisition.

The economic benefits of starting ART at a CD4+ count of ≤ 350 cells/mm³ are well established (36). A recent costing study based on South African data suggests that starting ART at higher CD4+ cell count (>500 cells/mm³) could yield potential cost-savings, but would require considerable “front loading” of investments (36).¹ Further economic and epidemiological modelling is needed to refine projections of the expected resource needs and public health impact of such recommendations in different settings. Further modelling is being done to examine the impact, costs and cost-benefits of investing in different types (and combinations) of HIV prevention and treatment interventions.

¹ The model suggests the approach could avert 3 million new HIV infections and reduce cumulative costs by US\$ 10 billion over 40 years.

3. Using antiretrovirals strategically and effectively: An incremental approach

Current evidence seems to support the trend towards earlier initiation of ART for clinical benefits and suggests the wider use of ARVs (including ART) as key components of combination HIV prevention. Doing so will require countries to review policies and operational issues, and take difficult programmatic decisions, especially in the context of limited resources.

Despite the recent progress, most low- and middle-income countries are yet to reach the “Universal Access” targets for HIV treatment coverage. New recommendations that ART be used to prevent HIV infections in discordant couples, along with consideration of providing lifelong treatment for all pregnant women and key populations living with HIV, would increase the number of people eligible for ART and widen the ART gap. This additional need is reflected in Fig. 1 (in Section 2). Nevertheless, over time we have seen an incremental expansion of ART, and a projection of this approach into the future may help guide country decision-making. Fig. 4 depicts a range of five scenarios for ART eligibility.

3.1 EVOLVING SCENARIOS

Scenario 1

Scenarios for ART recommendations have evolved in the past decade. In the early phase of the treatment rollout in low- and middle-income countries in 2002, there was a consensus to treat people who had clinically apparent HIV infection (stages 3 and 4) or who had CD4+ counts of 200 cells/mm³ or lower. Some countries have not moved beyond that threshold, primarily because of limited resources and capacity.

- In 2002, 6 million people were eligible for ART (using a CD4+ cell count threshold of 200/mm³), and less than 5% of them were receiving treatment. In 2011, in addition to the 8 million people on ART, an estimated 3 million people with CD4+ counts of less than 200/mm³ were still in need of ART.

Scenario 2

By 2010, the consensus had shifted. ART was being recommended for people with CD4+ cell counts of 350/mm³ or less, and for HIV-infected infants, people with TB and those with chronic active hepatitis B, regardless of their CD4+ cell counts.

- WHO's 2010 treatment guideline increased the number of people eligible for ART to about 15 million at the end of 2011.

Scenario 3

By 2012, the HIV prevention benefits of ART had prompted WHO to add serodiscordant couples¹ to the list of people deemed eligible for ART regardless of their CD4+ counts. At the same time there is an increasing trend towards offering ART to all pregnant women for life, irrespective of CD4+ cell count ("Option B+").² Decreasing ART costs and the likely clinical and programmatic advantages³ are encouraging this trend. It is biologically plausible that ART would also reduce the risk of HIV transmission in populations other than heterosexual couples. Even though the magnitude of that effect may differ, an offer of ART irrespective of CD4+ cell count therefore could also be considered for key populations in settings with high HIV transmission rates (including for HIV-positive sex workers, men who have sex with men, transgender women and people who inject drugs). Several countries with concentrated epidemics are currently exploring that option.

- Offering ART to these groups at all CD4+ levels would increase the number of people eligible for ART to 23 million.

Scenario 4

The findings of the HPTN 052 trial have spurred a shift towards earlier initiation of ART. WHO is currently conducting a systematic review of evidence of the broader clinical benefits of starting treatment in people with CD4+ counts higher than 350 cells/mm³, with a focus on the 350–500 CD4+ cell count range. Some countries have already moved their ART initiation threshold to ≤500 cells/mm³.

¹ The definition of a "couple" might be programmatically interpreted and applied in different ways. Although the HPTN 052 trial focused on heterosexual couples in stable relationships, it is plausible that a prevention benefit would occur whenever unprotected sex happens, including in casual relationships and in sex between men.

² The likely additional benefits of "Option B+" include providing effective treatment to the woman, protecting her infant early from HIV infection during her next pregnancy, and preventing sexual transmission of HIV to her partner. In addition, such an option simplifies operational issues, such as the procurement and supply chain management of ARVs.

³ They include health benefits for the woman, prevention of sexual transmission to her uninfected partner, and greater operational simplicity, especially in high-fertility settings.

- Approximately 25 million people would have been eligible for ART in 2011 if, in addition to including key populations at all CD4+ levels, the treatment threshold had been raised to 500 cells/mm³ in all countries.

Scenario 5

The final scenario involves a “test-and-treat” approach. This would entail regular screening of entire populations for HIV infection and offering immediate treatment to everyone found to be HIV-positive. The aim would be to identify individuals as early as possible after becoming infected, and to use ART to suppress their viral load to undetectable levels. The strongest argument for such an approach is its potential for eliminating HIV transmission, as suggested in some modelling exercises. However, models often do not capture country realities, and their assumptions may not necessarily reflect the complexities of scaling up and sustaining HIV diagnosis, treatment and care.

Nonetheless, a few countries, primarily ones with concentrated epidemics, are considering such an approach. Furthermore, given the concerns about the chronic inflammatory complications of HIV infection, it can be argued that it is good clinical practice to treat HIV infection as early as possible. At the same time, the clinical benefits of starting ART at CD4+ counts of above 500 cells/mm³ have not been firmly established, and WHO has not yet concluded its systematic review of the evidence. Important research is underway that will contribute to that body of evidence. The benefits and risks, and the implementation challenges of such an approach, will have to be carefully considered.

- In 2012, 32 million people in low- and middle-income countries would be eligible for immediate ART if a “test-and-treat” approach were adopted.

In addition, PrEP has the potential to prevent HIV acquisition in certain individuals. At the moment, particular attention is being paid to the possible role of PrEP in HIV discordant couples and in men and transgender women who have sex with men. Therefore, the use of PrEP would be considered as a “niche” intervention which, in certain circumstances, might *complement* the early initiation of ART.

Figure 4:
Scenarios for the incremental expansion of ARV provision to treat and prevent HIV



Note: The number of people eligible for ART under each of the 5 scenarios is based on estimates for the end of 2011. The total projected need for Scenario 1 is based on a combination of all people on ART at the end of 2011 and the estimated number of people living with HIV who had CD4+ counts below 200 cells/mm³.

ART, antiretroviral therapy; HIV, Human Immunodeficiency Virus; TasP, treatment as prevention.

3.2 NEW COMPLEXITIES AND CHALLENGES

Each of the scenarios involves new complexities and challenges. Indeed, widened eligibility has highlighted a range of practical and institutional difficulties. Late diagnosis remains common and most people still start ART only when their CD4+ cell counts have fallen well below the current, recommended eligibility thresholds. The HPTN 052 trial has proved that earlier initiation of ART can prevent HIV transmission. However, the potential prevention or clinical benefit of early initiation must be balanced against potential complications (such as ARV toxicity and the emergence of HIV drug resistance) and the additional burdens placed on health services.

While the treatment policies of a few countries still position them within Scenario 1, the majority of countries currently fit in Scenario 2. Several countries have shifted to Scenario 3 and are adding elements of TasP. Most of the latter have concentrated HIV epidemics. A few, though, are experiencing generalized epidemics, but they have already achieved high ART coverage levels. In 2011 WHO reviewed 72 published national and regional HIV treatment guidelines. Among the 64 low- and middle-income countries included in that review, 10 had guidelines that recommended offering ART to serodiscordant couples, while 12 had recommendations for implementing “Option B+” for pregnant women. However, the review did not determine the extent to which those guidelines were indeed being implemented. A few countries, most of them medium- or high-income, have begun implementing or are considering adopting Scenario 4. Currently, only one country – the United States – reflects Scenario 5 in its national treatment policy (37).

Current WHO guidelines broadly correspond with Scenario 3, which involves firm recommendations for a general eligibility threshold of ≥ 350 cells/mm³, and for offering ART to serodiscordant couples regardless of CD4+ cell count. WHO recommends that countries consider the implications of offering early ART to all pregnant women, and it has begun a systematic evidence review for “Option B+”. WHO also suggests that countries (primarily those with concentrated HIV epidemics) explore the feasibility of providing early ART to certain key populations. It has commissioned a systematic evidence review to assist in that process. WHO’s 2012 TasP updates propose that countries adopt an incremental approach that would involve rigorously scaling up ART programmes using a threshold of ≥ 350 cells/mm³, while identifying additional opportunities to optimize the prevention benefits of ART.

Box 1:

Deciding the priorities

In all settings, the priority should be to treat those people who are in greatest need of ART for their own health. Further expansion of treatment access would involve additional criteria, which probably would differ depending on the specific epidemic and country contexts. Those criteria might include maximizing prevention benefits (by targeting populations and settings where HIV transmission is concentrated) or exploiting practical opportunities (such as identifying the partners of people living with HIV and offering them ART or PrEP, as appropriate). Countries will also need to align their HIV priorities with their own broader health and development strategies; HIV investments need to contribute to broader national health targets.

Box 2:

WHO's latest treatment guidance and updates

WHO is monitoring emerging evidence on when to start ART and the role of ARVs in HIV prevention. Based on new evidence and country experiences, WHO issued new guidance and programmatic updates in 2012 to complement the 2010 WHO ART guidelines. These included:

- Guidance on couples' HIV testing and counselling and on the use of ART for HIV treatment and prevention in serodiscordant couples (38);
- A programmatic update on the operational aspects of using ARVs for treating pregnant women and preventing HIV infection in infants (39);
- A programmatic update on the use of HIV treatment as prevention of HIV and TB (TasP) (40);
- A guideline on PrEP¹.

WHO is currently working towards issuing consolidated guidelines in 2013 that will combine all ARV-related guidance, including using treatment for prevention and PrEP. For the first time, these guidelines will cover programmatic and operational issues to help countries take the best strategic decisions on the use of ARVs.

¹ In preparation

4. Making the most of the new opportunities

Changes are needed if the world is to progress from the current reality of limited and uneven ART uptake to one where ARVs achieve the maximum impact in equitable and sustainable ways. Scientific research is showing the huge potential benefits of a more ambitious scale-up of HIV treatment. Yet many countries are still struggling to take full advantage of the existing opportunities. Their experiences underline the fact that many of the approaches used up to now will not be sufficient in the future.

There is an urgent need to develop and refine new, simpler and more effective technologies and approaches if countries are to overcome current and future difficulties, so as to maximize and sustain the potential benefits of a massive ART scale-up. WHO, UNAIDS and partners have launched the *Treatment 2.0* strategy to help catalyze and guide these enhancements in several critical areas.

4.1 BETTER DRUGS AND USING THEM MORE EFFECTIVELY

Further optimization of drugs is needed if there is to be a rapid and sustainable expansion of treatment access, and broader use of ARVs for HIV prevention. The range of ARVs has expanded dramatically in the past 10 years with the development of new formulations, co-formulations and doses. There are ongoing studies to identify the best combinations of different ARV classes, dosing levels and sequencing for ART. At the same time, multiple potential short- and long-term side effects still complicate ART regimens, which compromise ART adherence and retention in care. The aim must be to arrive at ARV regimens that will be as safe, effective, tolerable, stable and convenient as possible.

There is potential for a range of improvements. ART regimens could be simplified further for delivery at primary health care level. Stronger harmonization is possible across the various ARV regimens that are recommended for infants, children, adolescents, adults, pregnant women and women of reproductive age. More suitable ARV formulations can and must be developed, particularly for infants. In addition, the most appropriate ARVs for PrEP have to be selected to prevent them from compromising ART regimens in the future.

Some short-term priorities

A great deal can be achieved with existing ARVs and recommended regimens. Short-term priorities include improved formulations and co-formulations of existing ARVs for both adults and children, harmonizing regimens across different populations, and reducing the number of preferred regimens to two options each for first- and second-line, respectively.

¹ The options are equivalent, and countries' decisions should be based on cost and availability.

Box 3:

The immediate priorities

- *Moving to a one-pill-a-day fixed-dose combination as the preferred first-line regimen for all populations.* Among ARVs currently available, the first-line ART option to be optimized and used for adults and adolescents is tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) or tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV)¹ in a fixed-dose combination.
- *Developing more protease inhibitor formulations that are heat stable to improve second-line regimens.* The development of a heat-stable, fixed-dose combination of atazanavir and low-dose ritonavir (ATV/r), combined with a nucleoside reverse transcriptase inhibitor (NRTI) backbone, can be an additional option to improve second-line therapy.
- *Improving paediatric first- and second-line ARV regimens and formulations.* There is an urgent need to move away from liquid paediatric formulations towards solid and fixed-dose formulations. This includes the use of sprinkles of heat-stable formulations of lopinavir/ritonavir (LPV/r), dispersible tablets of zidovudine/lamivudine (AZT/3TC), heat-stable formulations of ritonavir (RTV), and scored tablets of a dispersible fixed dose combination of TDF/3TC/EFV formulations.
- Progressive phasing out of more toxic drugs, such as stavudine.

There are opportunities to improve the alignment of adult ART regimens with the ARV regimens that are used for pregnant women. Practical experiences in countries underline some of the clinical and programmatic advantages of using triple ARV regimens in pregnant women who are HIV-positive, and in PMTCT of HIV. This confirms the advantages of using a “test-and-treat” approach in pregnant women (“Option B+”).

Some medium-term priorities

In the medium term, guidance should consider the broader benefits of earlier ART initiation – in particular the clinical benefits (i.e. the prevention of HIV-related morbidity and mortality, and of co-infections and co-morbidities such as TB and hepatitis B) and the reduction of HIV transmission. Operational aspects such as determining which regimens would facilitate and enhance treatment retention, should also be carefully considered. ARV regimen choices need to be guided by efficacy, tolerability, robustness and forgiveness, with no overlapping resistance in treatment sequencing, and they should be compatible with anti-TB and anti-hepatitis B and C treatments.

Box 4:

BOX 4: Medium-term priorities over the next 3–5 years

Developing and using fixed-dose combinations with new ARV drugs (including second-generation nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors).

- Developing and using new ARV classes (including integrase inhibitors and entry blockers).
- Aligning and harmonizing regimens (including first- and second-line regimens for adults, adolescents, pregnant women and children over the age of three years).
- Assessing the potential of new strategies (including induction-maintenance regimens, sustained-release once-a-week/month regimens, co-therapies and gene therapy).

WHO convened a group of experts in May 2012 for a “think tank” consultation to consider future medium-term opportunities for optimizing ARVs and ART regimens. Table 2 presents some of the options that could be considered for optimization of first- and second-line regimens, based on existing research and current ARV pipelines. The table is presented as a basis for further discussion. The consultation process with experts is ongoing and will inform WHO ART guidelines for 2013 and beyond.

Table 2:

Options under consideration for adult ART regimen optimization in the short- and medium-term

Regimens	Current recommended or potential short-term options	Potential optimization strategies in the medium term
NNRTI + 2 NRTIs	EFV + TDF + 3TC (or FTC) as an FDC	New NNRTIs New NRTIs Potentially ABC Reduced doses of EFV and TDF
bPI + 2 NRTIs	ATV/r or DRV/r + AZT + 3TC	Reduced doses of ATV, DRV and RTV DRV/r as heat stable FDC New NRTIs New PI boosters
bPI + InSTI	ATV/r or DRV/r or LPV/r + RAL	New InSTI DRV/r as heat-stable FDC Reduced doses of ATV, DRV and RTV New PI boosters
bPI + NNRTI	ATV/r or DRV/r + EFV	New NNRTIs DRV/r as heat-stable FDC Reduced doses of ATV, DRV, EFV and RTV New PI boosters
bPI ± entry blocker ± new/recycled drugs	ATV/r or LPV/r + MVC	DRV as heat stable FDC New NNRTIs New PI boosters Reduced doses of ATV, DRV and RTV Use of MRV without HIV tropism testing New entry blockers

3TC, lamivudine; ABC, abacavir; ATV/r, atazanavir/ritonavir; AZT, zidovudine; bPI, boosted protease inhibitor; DRV/r, darunavir/ritonavir; EFV, efavirenz; FDC, fixed-dose combination; FTC, emtricitabine; HIV, human immunodeficiency virus; InSTI, integrase inhibitor; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir; RTV, ritonavir.

Decisions on future guidelines require additional information about the long-term safety of ARVs in pregnancy and prolonged breastfeeding exposure to infants (including for TDF and integrase inhibitors). They also require dosing and safety data on boosted protease inhibitors and integrase inhibitors for children.

Possibilities for the improved prevention and treatment of HIV co-infections also need to be considered. They should include simplifying the management of HIV-related TB through daily dosing of rifabutin and co-formulation with other TB medicines, as well as the development of new hepatitis C antivirals for managing HIV and HCV co-infection. Cotrimoxazole and isoniazid preventive therapies will continue to be important and affordable components of TB prevention in people living with HIV.

More speculative, long-term perspectives (5–10 years away) include the possible development of drugs which a person would take for a short period and which could lead to a “sterilizing” cure or, if the infection were fully controlled but not eradicated, a “functional” cure.

Box 5:

Clarifying the efficacy and safety of ARVs

WHO recently released a series of technical updates on ART optimization that address concerns related to the efficacy and safety of certain ARVs, in order to help countries select the most effective ART regimens. These updates support:

- The interchangeability of lamivudine (3TC) and emtricitabine (FTC) (42). Current data support this from both clinical and programmatic perspectives;
- The safety of use of efavirenz (EFV) in pregnant women and women of reproductive age (43). The available safety data and programme experience support the EFV to optimize and simplify first-line treatment, including in pregnant women;
- The efficacy of tenofovir (TDF) in children and adolescents (44) has been established, but further research is needed on its long-term safety in the treatment of children aged two years and older, as well as operational research into the feasibility of implementing its use.

4.2 SIMPLER, FASTER AND LESS EXPENSIVE HIV DIAGNOSTICS AND LABORATORY SERVICES

There is a need for simplified, quicker, more reliable and more affordable technologies to achieve early diagnosis of HIV infection, and to assess the degree of immune impairment (which is done with CD4+ cell counts)¹, the intensity of viral replication (via viral load testing), the toxicity of ART (which is measured with haematology and chemistry tests), and drug resistance that may stem from ARV use.

There are opportunities to expand the use of existing, high-quality diagnostic and monitoring options. For example, rapid point-of-care HIV testing is increasingly available. As the use of point-of-care rapid HIV tests increases, priority should go towards improving the quality of those tests and the consistency of their use. Countries need to select appropriate tests, strengthen their regulatory capacities, and establish quality assurance and control systems. That should include the introduction of post-market surveillance to monitor the quality of diagnostics and the occurrence of adverse events.

The integration and efficiency of services can be improved with multi-disease diagnosis strategies and technologies. That might include bundling HIV testing with tests for associated conditions, and using single point-of-care testing platforms (including for the diagnosis of TB, syphilis, hepatitis B and C, and for haematology and clinical chemistry testing).

At the moment, access to CD4+ testing is insufficient and compromises decision-making for initiating ART, selecting PMTCT regimens and effectively monitoring patients on ART. Research shows that patients who get their CD4+ counts at the time of HIV diagnosis are twice as likely to start ART within three months, compared with those who have to return a week later for their results (46). These technologies also make it possible to reach marginalized populations more effectively, and to improve referral

WHO has released new guidance on the recommended standardized testing and re-testing strategies for high and low HIV prevalence settings (45).

¹ Large proportions of those who test HIV-positive do not return to clinics or hospitals for their CD4+ counts, and drop out of care until the onset of AIDS-related illnesses forces them to seek treatment. This is one of the main reasons why mortality rates are high during the first months of ART.

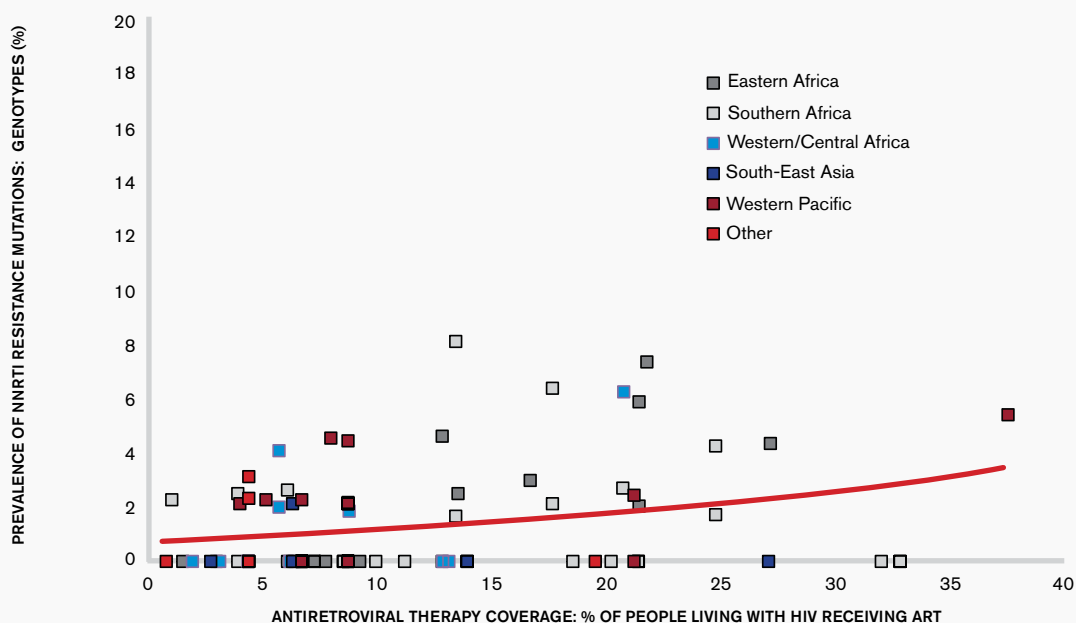
systems to HIV prevention and treatment services. Several point-of-care technologies are now available to determine CD4+ cell counts, and more technologies for assessing CD4+ cell counts and viral load are being developed.

More accessible new technologies for viral load testing are needed to enable earlier identification of ART failure and timelier switching of regimens. There is also an increased need for regular and reliable monitoring of possible ARV side effects and of the emergence of drug resistance. Simpler detection methods might make it cost-effective in some settings to assess individual HIV drug resistance, and could be used in those instances. As people continue on life-long treatment, the need increases for effective monitoring and decision-making about the timing of switches to the most appropriate second- and third-line ART regimens. It will become more important to confirm and choose which drugs are predicted to be most effective, according to the drug resistance patterns in the population. Concerns about drug resistance should not deter efforts to scale-up ART; levels of HIV drug resistance have remained modest during the dramatic scale-up of ART in the past 10 years (see Box 6).

Box 6:
Keeping watch on HIV drug resistance

Literature reviews suggest that the prevalence of transmitted drug resistance in low- and middle-income countries increased between 2003 and 2009 to 6,6% (5,1% to 8,3%). WHO surveys show that there is an association, albeit a weak one, between higher levels of ART coverage and increased prevalence of transmitted drug resistance to the NNRTI class of drugs (such as nevirapine or efavirenz) (see Fig. 5). The prevalence of HIV drug resistance among patients starting ART increased slightly, from 4.8% in 2007 to 6.8% in 2010.

Figure 5:
Relationship between resistance to NNRTI drugs and ART coverage



P-value adjusted for region= 0.039; Odds-ratio per 10% increase in ART coverage= 1.49 (95% C.I: 1.07 - 2.08)

HIV, human immunodeficiency virus; NNRTI, non-nucleoside reverse transcriptase inhibitor.

The evolution of drug resistance under ART suggests that it is a manageable problem. Among the more than 3 000 patients on first-line regimens in 40 WHO drug resistance surveys, 90% had viral suppression. Among those with detectable viral loads, 72% had resistance (mainly to nucleoside and non-nucleoside ARVs). It is essential that HIV drug resistance continues to be monitored carefully while ART programmes are scaled up.

Controlling the quality of these new technologies and assuring their appropriate use will require specific attention. Efficient regulatory processes, including the WHO prequalification system, will be needed for the rapid approval of new testing, CD4+ and viral load platforms.

Box 7:

Some immediate priorities

There are several short-term priorities (47), including:

- Quickly introduce available point-of-care technologies to measure CD4+ cell counts in settings where one can anticipate their efficient deployment (mainly in generalized HIV epidemic settings);
- Develop additional low-cost, rapid assays that require minimal instrumentation to determine CD4+ counts and to monitor viral load;
- Use dried blood spots to increase access to early infant diagnosis of HIV infection, viral load testing and HIV drug resistance testing when the collection of plasma samples is impossible or impractical;
- Validate the use of readers for rapid diagnostic tests in field situations and ensure that they have the ability to transmit data (by mobile telephone or the internet) for quality control and supply management purposes;
- Use new methods (including mobile telephone and internet technologies) to distribute results to clinicians and clients; and
- Develop combined rapid diagnostic tests for HIV and syphilis, and for HIV and hepatitis B.

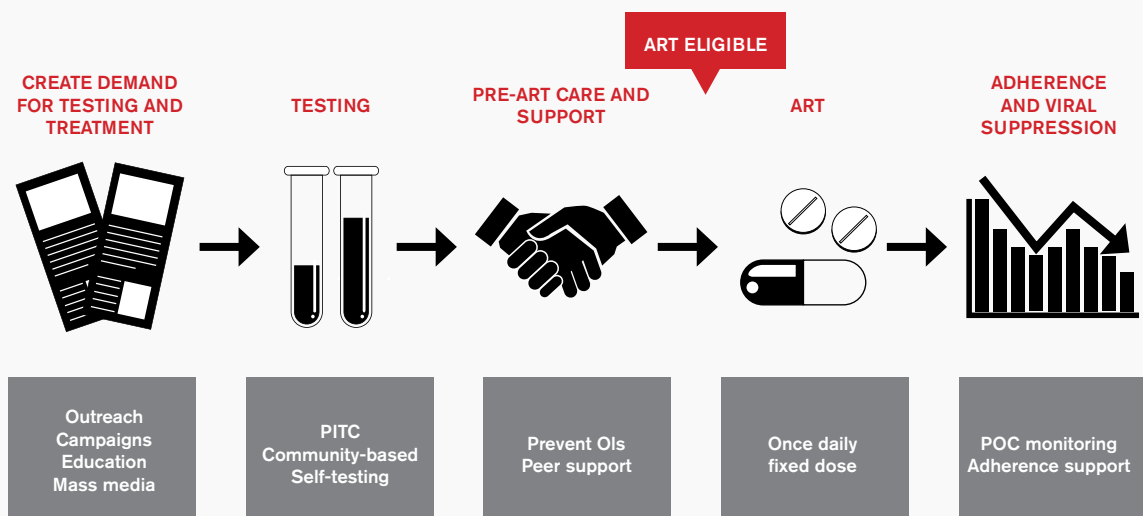
4.3 IMPROVED RETENTION, STRONGER LINKAGES, MORE DECENTRALIZATION AND MAXIMIZED HUMAN RESOURCES

Treating many more people, expanding PMTCT and introducing PrEP will require more efficient, acceptable and accessible health services. The public health approach to ART that has enabled the rapid expansion of HIV treatment over the past 10 years should underpin the further adaptation of health services.

Box 8:
THE “TEST-TREAT-RETAIN” CONTINUUM OF HIV CARE

Health services have to address the full continuum of HIV care. It extends from HIV testing, referral and enrolment in prevention and care services, to pre-ART care, ART eligibility testing, ART initiation and retention, and switching to second- and third-line ART regimens, all the way to palliative and end-of-life care. Each stage of that cascade, which is shown in Fig. 6, offers opportunities to minimize loss to follow-up and improve retention in care.

Figure 6:
The “test-treat-retain” continuum of care



ART, antiretroviral therapy; HIV, human immunodeficiency virus; PITC, provider-initiated testing and counseling; POC, point-of-care; OI, opportunistic infections

Expanded access and increased use of services

Service delivery models need to be adapted to support timely initiation of ART, retention in care across the continuum of care, and treatment adherence. In several settings, services may need to be reorganized to manage the increased numbers of people with HIV who are in chronic care. Treatment services should be convenient and acceptable for both patients and health-care providers. One way to achieve this is by continuing to decentralize services in high-burden settings in ways that bring them as close as possible to those in need. In concentrated epidemics and low burden settings where patient loads are small and capacity is limited, HIV-specific services that are provided in more centralized facilities may be more appropriate, less costly and more feasible.

HIV services are already being integrated by necessity at lower-level health facilities in high-burden settings. PMTCT services are becoming core elements of maternal and child health services, and there are moves towards greater integration of HIV services with TB, drug dependence and harm reduction services. If ART and other HIV interventions are integrated further into other health services, (in line with the country context and epidemic type), treatment access could conceivably keep improving.

As access to ART improves, HIV infection will increasingly become a chronic manageable condition and people with HIV will develop noncommunicable diseases, some of which may be related to HIV disease, ageing or ARV complications. Close links between HIV services and noncommunicable disease programmes therefore will become more important.

In settings with high HIV prevalence, a team approach for delivering chronic HIV care and for decentralizing and integrating services often requires shifting selected tasks from more specialized to less-specialized health workers and primary-care providers. Such task shifting should also be used to deal with growing workloads of health care workers associated with increasing numbers of people in care. Task shifting needs to be complemented by expanded, outreach services, peer support initiatives and community-based programmes.

New WHO guidelines recommend that HTC should be offered to couples in various health-care settings. This would create more opportunities for offering ART to prevent HIV transmission in serodiscordant couples. Such an approach would also boost the benefits of couples testing together (such as increased uptake and adherence to ART and PMTCT) (38). WHO has developed simple HIV testing strategies for different epidemic contexts and settings, using the best available technologies.

Box 9:

Helping more people make better use of HIV testing

Much better access to quality HIV testing is required to identify those who would benefit from ARVs as early as possible. Multiple models of HIV testing and counselling (HTC) are being implemented. They include provider-initiated testing and counselling (PITC) in clinical settings, stand-alone, voluntary HTC sites, and community-based services (such as home-based, outreach and workplace programmes).

HTC continues to be provided in health-care facilities and there is increasing acceptance of routine offers of testing when the PITC approach is used. This has led to increased uptake of HTC in clinical settings, particularly in antenatal and TB clinics (48). However, there are important opportunities to increase access to testing through PITC in all clinical settings, especially in high-prevalence, generalized epidemics.

In addition to expanding and diversifying facility- and community-based HTC services, innovative models of HTC will need to be assessed, developed and supported. They might include self-testing, multi-disease testing campaigns, and mobile and outreach HTC for marginalized populations. Well-functioning quality assurance systems will be essential to ensure correct test results. The introduction of PrEP will also require clear guidance on re-testing.

Retaining more people in care

Linking people up to HIV care and retaining them is vital to maximize the prevention and treatment benefits of ARVs, and to minimize the development of HIV drug resistance. This is a challenge, since patients have to be retained throughout the continuum of care (see Box 8). Considerable improvements are needed.

Expanded access to HTC provides a critical entry point into the care continuum. Yet the majority of people living with HIV are unaware of their infection. Also, many current HIV testing models fail to link those who are diagnosed with HIV to adequate care. Stronger linkages between HTC and HIV care services can minimize patient attrition before enrolment in pre-ART care. This is especially challenging for community-based HTC, where established referral systems may be absent or weak. Promoting expanded HIV testing and earlier HIV diagnosis, along with better linkages to care, are key aims of the new WHO strategic HTC framework (45).

Other current weaknesses include loss-to-follow-up before patients initiate ART and poor monitoring once treatment starts. Developing services that fit their contexts, are acceptable to patients, harness community support structures and organizations, and use mobile technology and point-of-care diagnostics can significantly improve patient retention (49).

Once patients become eligible to initiate ART, providing counselling and support to improve treatment literacy and prepare them for ART may reduce attrition. Barriers to ART initiation should be minimized. This can be done by reducing waiting lists and clinic waiting times, and by rationalizing the number of visits needed for assessment and adherence counselling (50).

Retention in care can be improved with user-friendly services that have convenient operating hours, are close to where people live, have well-trained and understanding staff, and provide free services at the point of care. Stronger patient record systems and the use of new communication technologies would enhance patient tracking. Simplified patient monitoring would minimize clinic visits and relieve the burden on health services. Improved treatment regimens would enhance their acceptability and strengthen adherence and retention on ART.

Generally, the principles of effective chronic disease management should be applied, including the active engagement of patients themselves, their families and the broader community.

4.4 LOWER PRICES AND REDUCED COSTS

ART costs need to decrease further if the scale-up of treatment is to be sustained. There have been dramatic reductions in the price of ARVs over the past 10 years (see Figs. 7 and 8). The average cost of one year's supply of first-line ARVs fell from more than US\$ 10 000 per person in 2000 to US\$ 160–200 in 2011 for the currently preferred WHO regimens (tenofovir/lamivudine/efavirenz or tenofovir/emtricitabine/efavirenz) – a reduction of almost 98% (51). This is due to a range of factors including economies of scale made possible by growing demand, competition between drug manufacturers (especially producers of generic drugs), reduced procurement costs and determined advocacy by activists and multilateral agencies.

Figure 7:
Median prices of WHO-recommended first-line regimens in low- and middle-income countries, 2004–2012 (US\$ per patient-year)

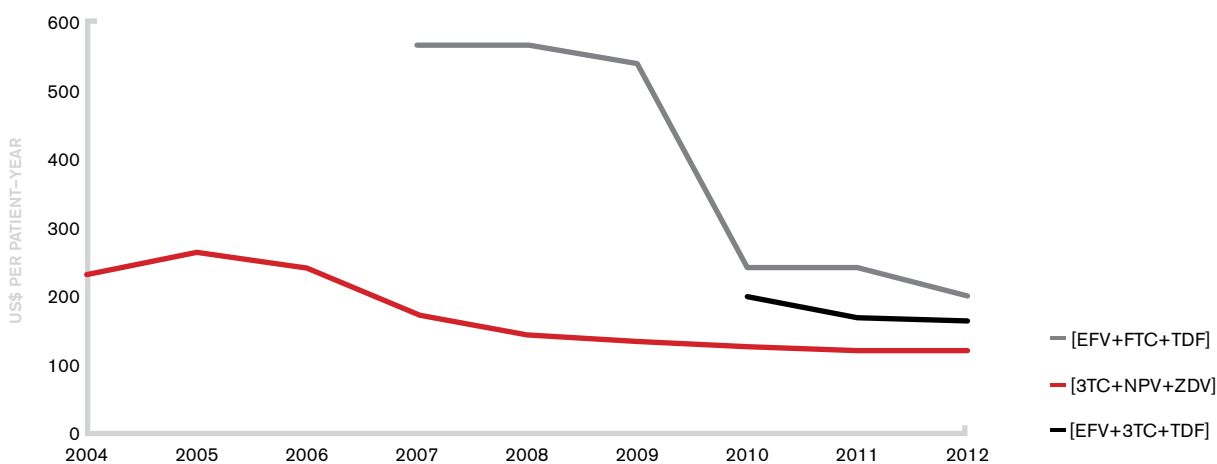
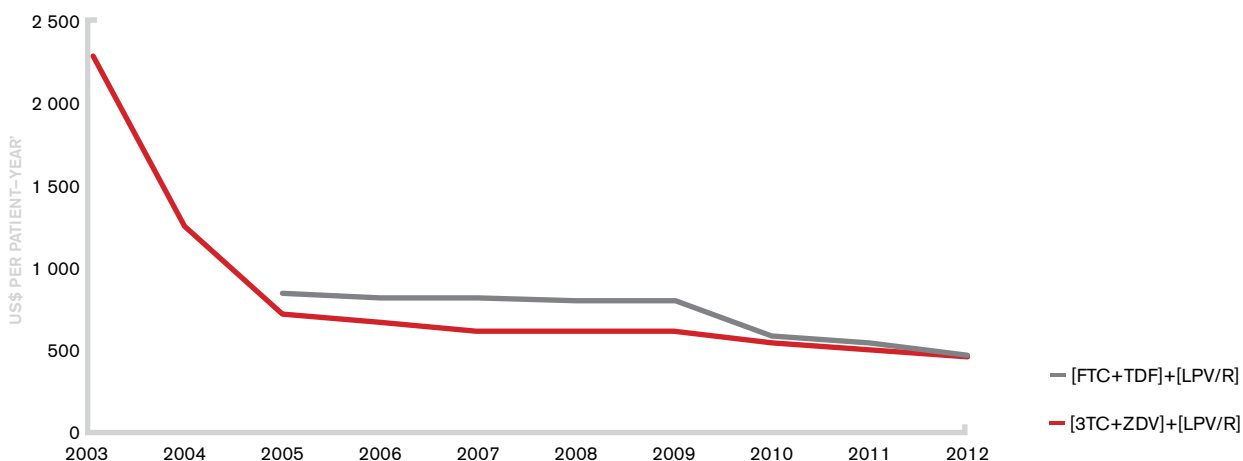


Figure 8:
Median prices of WHO-recommended second-line regimens in low- and middle-income countries, 2003–2012 (US\$ per patient-year)



3TC, lamivudine; EFV, efavirenz; FTC, emtricitabine; NVP, nevirapine; TDF, tenofovir; ZDV, zidovudine
 3TC, lamivudine; FTC, emtricitabine; LPV/R, lopinavir/ritonavir; TDF, tenofovir; ZDV, zidovudine

Despite these price reductions and increasingly efficient service delivery, the cost of ART remains a major barrier to further, possibly massive, treatment scale-up. These costs are determined by the price of ARVs and diagnostics, and by the cost of service delivery and programme management. There are opportunities for further savings in each of these areas and for ensuring increased access to new, better and more affordable ARVs (52,53).

For generic ARVs, the market product price comprises the cost of the active pharmaceutical ingredients (APIs), labour, the formulation and packaging costs, indirect costs and a percentage for profit (54). The cost of several ARVs can be reduced through improved and new API manufacturing processes and by sourcing cheaper raw materials. Further reductions could be achieved by decreasing the amount of APIs being used (for example, through dose reduction, product reformulation to increase bioavailability, and the use of boosting agents such as cobicistat). Strategies for extending ARV shelf life and simplifying transportation and storage arrangements can help reduce programme costs.

Costs can also be reduced by influencing ARV and diagnostics market dynamics. Increased competition from generic manufacturers has been instrumental in the price decreases observed in the past decade; it is essential to preserve the ability of generic producers to supply the ARV market. This might require using flexibilities in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), and promoting mechanisms to stimulate product development (such as patent pooling). Additional options include improving market efficiencies (through more accurate demand forecasting), increasing the transparency of diagnostics transaction prices, implementing pooled procurement systems, and providing incentives for manufacturers to innovate and produce products for less-profitable markets. Finally, with the increasing reach and importance of intellectual property protection – including on medicines – negotiation with originator pharmaceutical companies about how their new products will reach low-income markets will become more important for guaranteeing wide and equitable access to innovation.

It is estimated that service delivery accounts for over 50% of ART costs in most low- and middle-income settings. More efficient service delivery is therefore critical. Lowering the cost of other services (such as tests for monitoring treatment) and reducing indirect expenses (for example, transportation) would also improve treatment uptake and retention by reducing patients' out-of-pocket expenses. While efforts are needed to increase efficiencies and reduce costs wherever possible, they must be balanced with careful attention to assuring quality. No compromise on quality is acceptable.

4.5 AN ETHICAL AND EQUITABLE APPROACH

The selection of the most appropriate interventions and allocation of resources must be guided by core ethical, equity and rights-based principles. Given the large number of people in need of ART, each country has to plan a fair and equitable approach to expand access to ART.

While it is recognized that a lack of access to treatment is a breach of people's fundamental right to health, there is also a general consensus that the top priority should be to treat those who are in the greatest need. Beyond that, country contexts should guide ART scale-up, taking into consideration the most efficacious interventions, which populations are most vulnerable and most at risk, and where the greatest impact can be achieved. The feasibility and sustainability of different interventions, and health system capacity and costs will also have to be taken into account. WHO has been working with human rights activists, community experts, economists and programme managers to develop and cost an essential human rights and community-support package for HIV programmes (55).

The rapid expansion of HIV testing, for example, addresses a range of ethical and human rights issues (including the need to know one's HIV status in order to make informed decisions about protecting one's own health and that of others). But it also involves challenges, such as guaranteeing informed consent and confidentiality, and achieving a supportive environment that minimizes the risks of stigma and discrimination. Meanwhile, using ARVs to prevent onward transmission to uninfected partners raises new ethical issues, including those of providing relatively healthy people with potentially toxic drugs for prevention benefits to others. Further ethical issues relate to the use of ARVs for wider HIV prevention (including PrEP) while treatment coverage remains low.

4.6 SOLID EVIDENCE AND STRONG POLICIES

Strong political commitment at all levels, sound national strategies and plans, and increased external and domestic investment made the treatment scale-up possible during the past decade. Although national ART policies vary considerably, in isolation they are not enough to assure impact. Policies need to be accompanied by determined efforts to deliver quality services to all in need, and by adequate resources to achieve this goal. This involves important programmatic and allocation decisions.

Box 10:

Selecting the most cost-effective strategies

The global financial crisis, coupled with the existence of competing health and development priorities, underscores the need to demonstrate the longer-term public health, economic and development benefits of immediately “front-loading” investments for expanded ART and PrEP.

Such an approach needs to be supported by evidence on the clinical and epidemiological benefits of earlier initiation of ART, its safety (in terms of toxicity and drug resistance), and the HIV prevention impact of ART in different populations. Modelling indicates that increasing coverage of ART would be cost-effective in the short term and could even be cost-saving in the longer term. A recent exercise in Haiti, for example, showed early ART (starting at CD4+ counts of less than 350 cells/mm³) would be cost-beneficial within three years (56).

Comparisons of the cost-effectiveness and cost-benefits of different ARV-based interventions (including expanded use of ART, universal access to ART for specific populations, as well as PrEP and other prevention interventions) should be used to help inform planning and resource allocation. It is important, however, to incorporate local data in modelling assumptions when trying to arrive at cost-effectiveness and cost-benefit estimates for decision-making.

Finally, it is also important to show that those benefits extend beyond improved HIV outcomes and include other health outcomes (such as TB and maternal and child health), strengthened health systems and greater health equity. Although health outcomes are critical, the potential social and economic benefits of expanded ART access (including increased productivity) are also important. Until very recently, economic analyses focused primarily on a health system perspective; they will need to expand to encompass societal and individual perspectives as well.

The available evidence¹ shows that initiating treatment at ≤ 350 CD4+ cells/mm³ reduces HIV-related disease progression. However, it is not yet clear whether there is a corresponding reduction in mortality. In the coming years, several ongoing randomized clinical trials (including the TEMPRANO and START trials) (57,58) are expected to provide additional findings that may clarify such questions.

Morbidity and survival gains, however, are no longer the only considerations that should inform decisions relating to ART; the assessment of benefits should also include the potential impact on HIV prevention. Several observational studies from British Columbia (Canada) (59), San Francisco (USA) (60), Taiwan (China) (61) and South Africa (24) have documented reduced HIV transmission at population level with expanded ART coverage. In the British Columbia and San Francisco studies, this was associated with providing ART regardless of CD4+ cell count. Additional empirical data will be valuable and are expected to emerge from a range of ongoing studies, including several “combination prevention” trials.

Modelling exercises can also inform policies, programmes and resource allocation decisions. They can be especially useful to help determine costs and to decide where the expanded use of ARVs would have the greatest impact in reducing HIV incidence, morbidity and mortality. They can also inform a step-wise approach to scale-up and help determine the relative mix and targeting of ARV use. For example, which interventions should be pursued (ART, PMTCT, PrEP and/or PEP), which populations should be prioritized (people who use drugs, men who have sex with men, sex workers and/or discordant couples), which settings should be targeted (such as areas with high HIV incidence and prevalence), which co-morbidities should become priorities (viral hepatitis and TB, for example), and more. The evidence base for these kinds of decisions is expected to grow substantially in the next few years.

Finally, the strategic use of ARVs needs to be positioned within a broader and comprehensive HIV response. ART should be used in concert with evidence-based combination HIV prevention, comprehensive HIV care, and behavioural and structural interventions to ensure the long-term acceptability and sustainability of programmes.

¹ Mostly from several multicentre observational studies in North America and Europe, as well as from the randomized control HPTN 052 trial.

5. Moving forward: WHO's strategic approach

The HIV epidemic is evolving and the opportunities for responding to it are changing rapidly. HIV planners and programme managers therefore constantly have to assess new developments and take the most appropriate decisions about:

- Combining ARV-based and other interventions;
- Delivering them in quality-assured and equitable ways; and
- Prioritizing and allocating resources as growing numbers of people become eligible for ART.

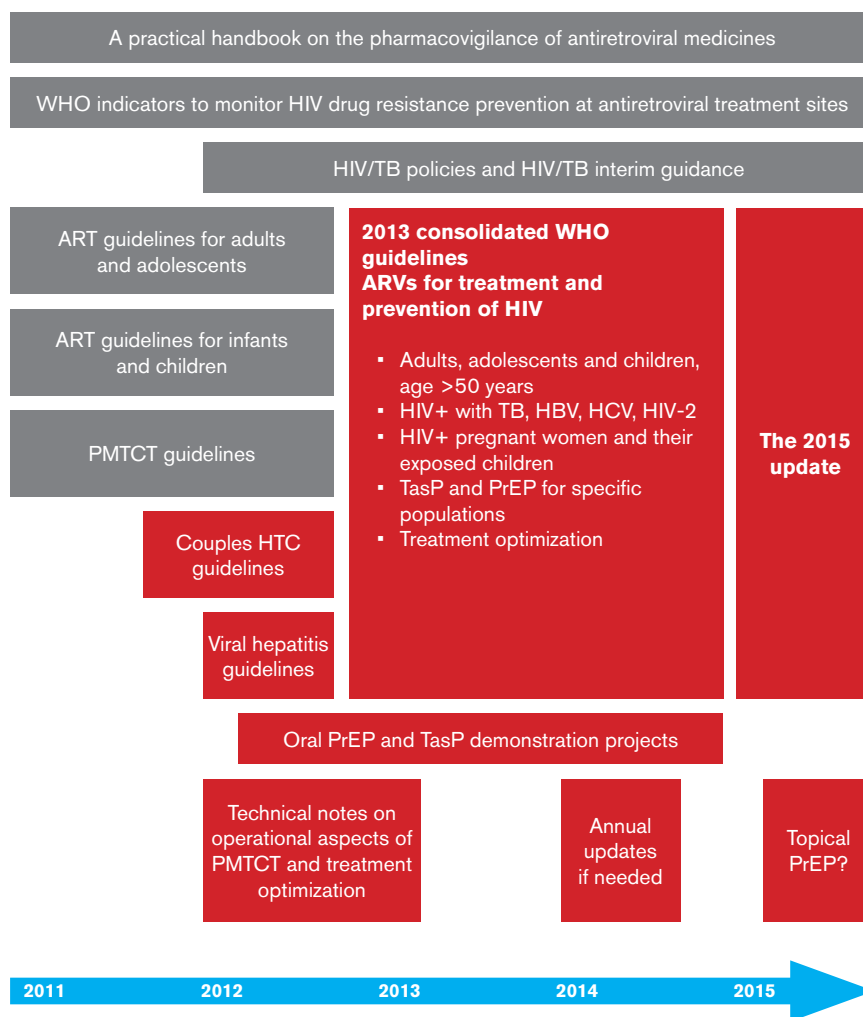
WHO plays an important role supporting such decision-making, and translating new evidence and technical innovations into concrete guidance for countries (see Fig. 9).

WHO revised its treatment guidelines in 2010, by expanding the treatment indications from a CD4+ cut-off point of 200ml/mm³ to 350ml/mm³. In 2011 it launched the *Treatment 2.0* initiative with UNAIDS.

WHO has responded to the latest research evidence with further guidance. This includes recommendations on the use of ARV treatment-as-prevention (TasP) in serodiscordant couples, a programmatic update on TasP, a PMTCT update and a policy statement on HIV/TB collaborative activities (which discusses the use of TasP to prevent TB), as well as recommendations related to the use of ARVs as PrEP.

WHO will also release recommendations on the use of pre-exposure prophylaxis (PrEP). These will recognize the potential role of PrEP in combination HIV prevention approaches and recommend that it be considered for use in carefully controlled pilot settings.

Figure 9:
Recent and future WHO publications giving ARV-related guidance



ART, antiretroviral therapy; ARV, antiretroviral drugs; HBV hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HIV-2, human immunodeficiency virus type 2; HTC, HIV testing and counseling; PMTCT, prevention of mother-to-child transmission; PrEP, pre-exposure prophylaxis; TasP, treatment as prevention; TB, tuberculosis.

5.1 COMING SOON: THE NEXT GENERATION OF ARV-RELATED GUIDELINES

The *Global Health Sector Strategy on HIV/AIDS, 2011–15* provides a comprehensive framework to guide national health sector strategies for HIV diagnosis, prevention, treatment and care, and outlines WHO's priorities over this five-year period (62). It includes a specific programme of work for WHO related to the strategic use of ARVs. Over the next five years, this programme will focus on two key areas:

- Optimizing HIV treatment scale-up through the *Treatment 2.0* framework, and
- Providing guidance on the strategic use of ARVs through a set of consolidated ARV guidelines.

Recent developments require the revision of WHO's guidelines, which is ongoing. Systematic reviews are being conducted to inform the new guidelines, which will be released during 2013. There is an opportunity to harmonize ART regimens across different populations. The revision process will gather all ARV-related recommendations (including those on the use of ARVs for HIV prevention) into a single set, which will constitute consolidated guidelines on the strategic use of ARVs in all aspects of HIV treatment and prevention.

- WHO intends to update the consolidated guidelines every two years. When necessary, rapid guidance and technical and operational updates will complement the biennial updates.

ARV programmes face a range of operational challenges, including the need to use limited resources as effectively as possible by selecting the most suitable interventions and technologies. The new generation of WHO guidelines will therefore include operational and *programmatic* guidance, in addition to the customary *clinical* guidance.

- The **clinical component** of the guidelines will adopt a continuum-of-care approach. It will make recommendations on the diagnosis of HIV infection; the use of ARVs in HIV prevention; pre-ART care; initiation and maintenance of first-, second- and third-line ART regimens; monitoring for treatment failure, ARV toxicity and HIV drug resistance; management of co-infections and co-morbidities; and prevention and management of drug interactions. The needs of specific populations (such as pregnant women, children, drug users, people with TB or active hepatitis) will be addressed in special sections.

- The **operational component** will describe how ARV programmes can be implemented most efficiently and effectively. It will include recommendations on HIV testing approaches and strategies; models of chronic care; integration of HIV treatment and care with other services; decentralization of services; community engagement; task shifting; adherence to ART; and retention in care.
- The **programmatic component** will provide guidance on how to support the translation of clinical and technical recommendations into policy and practice at national and local levels, as well as guidance on what parameters to consider when setting priorities and deciding on the implementation of the new recommendations. Strategic information needs will be addressed throughout the guidelines, including monitoring and evaluation of programmes, and operational research.

A further, anticipated evolution of the guidelines will entail the endorsement of a rapid roll out of point-of-care CD4+ count technologies in areas where access to CD4+ cell counts is lagging, along with increased reliance on viral load testing to monitor treatment.

5.2 KEEPING PACE WITH NEW DEVELOPMENTS

The 2013 consolidated guidelines will reflect the most current knowledge, available medicines, diagnostics and good practices for service delivery. However, HIV treatment is evolving rapidly and new products and approaches will continue to become available after 2013. WHO needs to anticipate what guidance might be required for 2015 and beyond.

The *Treatment 2.0* framework provides an opportunity to look into the future, promote innovation and prepare long-term and sustainable strategies. WHO has established work streams to move ahead on HIV drug optimization, simplified and reliable HIV diagnostics, and more efficient and effective service delivery. In each of those areas, attention will be devoted to reducing costs, achieving high-quality standards and maximizing community engagement.

As HIV infection becomes a chronic manageable condition, and with the prospect of many millions of people staying on life-long treatment, chronic care models will need to be developed for different country contexts and populations. The integration and linking of HIV services with other health services will become ever more critical. The increasing importance of linkages between HIV and noncommunicable diseases, particularly for ageing populations living with HIV, will also need to be reflected in future HIV and noncommunicable diseases strategies and programmes.

6. Conclusion

Historic opportunities are at hand to end the HIV epidemic. Crucial among them is the expanded, strategic use of ARVs, and especially of ART. The safety and efficacy of ART has improved dramatically, and an impressive and growing body of research shows that it significantly prolongs lives and prevents new HIV infections, particularly with early treatment initiation. The latest research findings herald the genuine prospect of ending the HIV epidemic.

A decade of remarkable treatment scale-up in low- and middle-income countries has yielded important experiences and lessons on how to bring the benefits of ARVs to ever-increasing numbers of people. Systems and strategies are improving, capacities are being strengthened, and service delivery methods are being refined. A solid platform is being built.

There is also a better understanding of the aspects that require new and more durable solutions. Eventually, all people living with HIV will become eligible for ART. New knowledge about how to optimize the clinical and preventive benefits of ART has led to an incremental increase in the number of people living with HIV who are eligible for ART. In the coming years, it is likely that greater numbers of people will become eligible for treatment earlier in the course of HIV infection. They will need to have access to ART, and they will have to be retained on ART.

Yet even in the current eligibility scenarios, close to half of the people needing ART are not receiving it. Simply continuing with the approaches used up to now will not be adequate. Seizing the new opportunities will require well-informed and forward-looking policies, innovative solutions to implementation challenges, and further investments in the systems that are needed to support earlier initiation of treatment and long-term retention on it.

People with HIV should be diagnosed and should start ART in greater numbers and at an earlier stage. And they need to be retained in ART programmes to realize the maximum, long-term benefits. Alternatives to health facility-based HIV testing must be explored, and simpler, less expensive and better drugs and diagnostic tools (ideally available at points-of-care) need to be developed.

At the same time, more resolute efforts are needed to dismantle social and structural barriers to treatment and care, especially those that limit access for key populations (such as stigma, discrimination and punitive legal frameworks). In doing all this, important ethical and equity issues have to be addressed, which will require close community participation in the design and implementation of treatment programmes.

Expanding ART in ways that take full advantage of the potential benefits also has important resource implications. Modelling exercises show that “front-loading” treatment investments over the next five years would lead to cost-savings in the medium- to long-term, and would yield major societal gains in terms of infections averted and regained productivity.

These are grand challenges, but so is the opportunity to end the HIV epidemic at last.

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