

4. TREATMENT AND CARE FOR PEOPLE LIVING WITH HIV

Key findings

- At the end of 2009, 5 254 000 people were receiving antiretroviral therapy in low- and middle-income countries, an increase of over 1.2 million people from December 2008. This represents a 30% rise from a year earlier and a 13-fold increase in six years. Sub-Saharan Africa had the greatest increase in the absolute number of people receiving treatment in 2009, from 2 950 000 in December 2008 to about 3 910 000 a year later.
- As of December 2009, eight low- and middle-income countries had already achieved universal access to antiretroviral therapy, defined as providing antiretroviral therapy to at least 80% of patients in need, and 21 additional countries had coverage rates higher than 50%.
- WHO now recommends that adults and adolescents initiate antiretroviral therapy at an earlier stage of disease. WHO's revised antiretroviral therapy guidelines recommend that all adults and adolescents, including pregnant women, with HIV infection and a CD4 count of or below 350 cells/mm³ should be started on antiretroviral therapy, regardless of whether or not they have clinical symptoms. This change has increased the number of people estimated to be in need of antiretroviral therapy at the end of 2009, from 10.1 million to 14.6 million [13.5 million-15.8 million].
- As of December 2009, 45 countries had already incorporated into their national treatment guidelines the new WHO recommendations on eligibility criteria and regimen choice for adults and adolescents, and 33 had already started implementing stavudine (d4T) phase-out plans.
- Coverage of antiretroviral therapy in low- and middle-income countries rose further in 2009. Based on the new set of criteria for treatment initiation, coverage increased from 28% [26-31%] in December 2008 to 36% [33-39%] at the end of 2009. Under the previous criteria for treatment initiation (CD4 count at or below 200 cells/mm³), global coverage would have reached 52% [47-58%] in 2009.
- The number of children under 15 years of age receiving antiretroviral therapy increased by 29% between 2008 and 2009. About 356 400 children less than 15 years of age were receiving antiretroviral therapy at the end of 2009, up from 275 300 at the end of 2008. Children represented 6.8% of people receiving antiretroviral therapy and 8.7% of people in need.
- Among 95 reporting countries, antiretroviral therapy coverage was higher among women, estimated at 39%, compared to 31% among men.
- Data on the proportion of patients retained on antiretroviral therapy over time continued to show that most patient attrition occurs within the first year of initiation of therapy and that retention rates tend to stabilize thereafter. In 2009, the average retention rate at 12 months across low- and middle-income countries was 82%.
- More evidence is now available of the positive impact of antiretroviral therapy on HIV transmission, and additional research is ongoing to identify and assess policy and operational implications.
- Twenty-eight countries have completed surveys or are in the process of implementing them to classify the extent of transmitted HIV drug resistance. Quality assured results are available for 15 surveys. In 13 of these, transmitted HIV drug resistance was classified as low (<5%) and in two it was classified as moderate (between 5% and 15%).
- Further, but limited, reductions in the prices of first-line regimens occurred between 2008 and 2009. However, the price of second-line regimens remained considerably higher than that of first-line regimens. In 2009, the weighted median price of the six most widely used first-line regimens was US\$ 137 per person per year in low-income countries, US\$ 141 in lower-middle-income countries and US\$ 202 in upper-middle-income countries. For the most commonly used second-line regimens the weighted median per person per year was respectively US\$ 853, US\$ 1378 and US\$ 3638.
- In low- and middle-income countries outside of the Americas (59 reporting countries), 97.5% of adult patients were on first-line regimens and 2.4% were receiving a second-line regimen. In the Americas Region (17 reporting low- and middle-income countries), 84% of adults were receiving a first-line regimen, 9.7% were being treated with a second-line regimen and 6.3% were on salvage therapy.
- There has been progress in expanding HIV testing and counselling for tuberculosis (TB) patients over the past years. Almost 1.4 million TB patients knew their HIV status in 2008, accounting for 22% of notified cases compared to 16% in 2007 and 3.2% in 2004. However, antiretroviral therapy coverage among people living with HIV and TB was low, and implementation of the *Three I's for HIV/TB* – intensified TB case finding among HIV patients, isoniazid preventive therapy and TB infection control – remained insufficient.

In spite of the severe downturn experienced by the world economy in 2009, countries and partners involved in the global AIDS response continued to deliver solid achievements. An additional 1.2 million people were receiving life-saving antiretroviral therapy in low- and middle-income countries in 2009, bringing the total number of people on treatment in resource-limited settings to 5.25 million. This is a thirteen-fold increase from the approximately 400 000 patients recorded in December 2003. Furthermore, 2009 also witnessed a number of key technical developments that considerably altered the way antiretroviral therapy is implemented.

Accumulated evidence on the need to initiate antiretroviral therapy at an earlier stage of HIV infection and on the appropriateness of phasing out the use of stavudine (d4T) as a preferred option due to its well-documented long-term toxicities prompted WHO to update, through a broad consultative process, its antiretroviral treatment guidelines for adolescents and adults. Currently, all adolescents and adults, including pregnant women, with HIV infection and a CD4 count at or below 350 cells/mm³ should be

started on antiretroviral therapy, regardless of whether they have clinical symptoms (Box 4.1). Moreover, people living with HIV and TB should initiate antiretroviral therapy irrespective of CD4 count. These changes are important steps towards lowering excess morbidity and mortality, improving clinical outcomes and strengthening overall programme effectiveness. Clear evidence also emerged on the positive impact that antiretroviral therapy has on the prevention of HIV transmission. Although more technical and financial resources will be needed to implement the revised WHO treatment guidelines, considerable cost savings are likely to be realized over the long term in terms of reduced hospitalizations, deaths and HIV transmission.

In addition to rapidly scaling up access to antiretroviral treatment for the proportion of patients who still do not have access, countries also face the challenge of sustaining and managing existing programmes. In this respect, in a context of global fiscal constraints, it is critical to enhance the efficiency and effectiveness of the global AIDS response, while closely monitoring the quality of service delivery to promote and ensure optimum adherence and retention levels.

Box 4.1. New WHO guidelines for antiretroviral therapy in resource-limited settings

In response to the emergence of new scientific evidence, in December 2009 WHO updated its antiretroviral therapy guidelines for adults and adolescents. According to the new guidelines, which were developed in consultation with multiple technical and implementing partners, all adolescents and adults, including pregnant women, with HIV infection and a CD4 count at or below 350 cells/mm³ should be started on antiretroviral therapy, regardless of whether or not they have clinical symptoms. Those with severe or advanced clinical disease (WHO clinical stage 3 or 4) should start antiretroviral therapy irrespective of CD4 cell count. According to a recent WHO survey, several countries have already updated their national treatment guidelines to reflect this shift towards earlier initiation of antiretroviral therapy (see section 4.1.6).

Recommendations for first- and second-line treatments have also been updated. First-line therapy should consist of a non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTI), one of which should be zidovudine (AZT) or tenofovir (TDF). Countries should take steps to reduce the use of d4T in first-line regimens because of its well-recognized long-term toxicities. The new guidelines maintain the standard recommendation for second-line therapy, which should consist of a ritonavir (RTV)-boosted protease inhibitor plus two NRTIs, one of which should be AZT or TDF, based on what was used in the first-line regimen. Ritonavir-boosted atazanavir (ATZ) or lopinavir/ritonavir (LPV/r) are the preferred protease inhibitors. Patients coinfecting with HIV and TB should be started on antiretroviral therapy as soon as possible after starting TB treatment, ideally within the first eight weeks, irrespective of the CD4 cell count. The same applies to patients with HIV and chronic active hepatitis B (Box 4.12) (1–7).

4.1. Antiretroviral therapy

4.1.1. Global, regional and country progress in access to antiretroviral therapy

At the end of 2009, 5 254 000 people were receiving antiretroviral therapy, an increase of over 1.2 million¹ people from December 2008 (Table 4.1 and Figure 4.1).

As the region most affected by the epidemic, sub-Saharan Africa recorded the greatest increase in the absolute number of people receiving treatment in 2009, from 2 950 000 in December 2008 to about 3 911 000 a year later – a 33% increase. In Eastern Europe and Central Asia, the number of people on treatment rose by 34%. In December 2009, 114 000 people were receiving antiretroviral therapy versus 84 400 at the end of 2008. In all other regions, with the exception of Latin America, growth rates were reasonably homogeneous, at around 30% per year.

In Latin America, the increase in the number of people receiving antiretroviral therapy in 2009 vis-à-vis 2008 was relatively more modest, about 6%. This is explained by the fact that most large countries in the region have already achieved relatively high levels of coverage.

¹ This figure is likely to underestimate the exact number of people who initiated antiretroviral therapy in 2009 as some have died or discontinued antiretroviral therapy since initiation. The total number of people starting antiretroviral therapy in a year is not reported by countries; rather, only the number of patients alive and on antiretroviral therapy at the end of the reporting period is provided.

Table 4.1. Number of adults and children (combined) receiving and needing antiretroviral therapy, and percentage coverage in low- and middle-income countries by region, December 2008 to December 2009^a

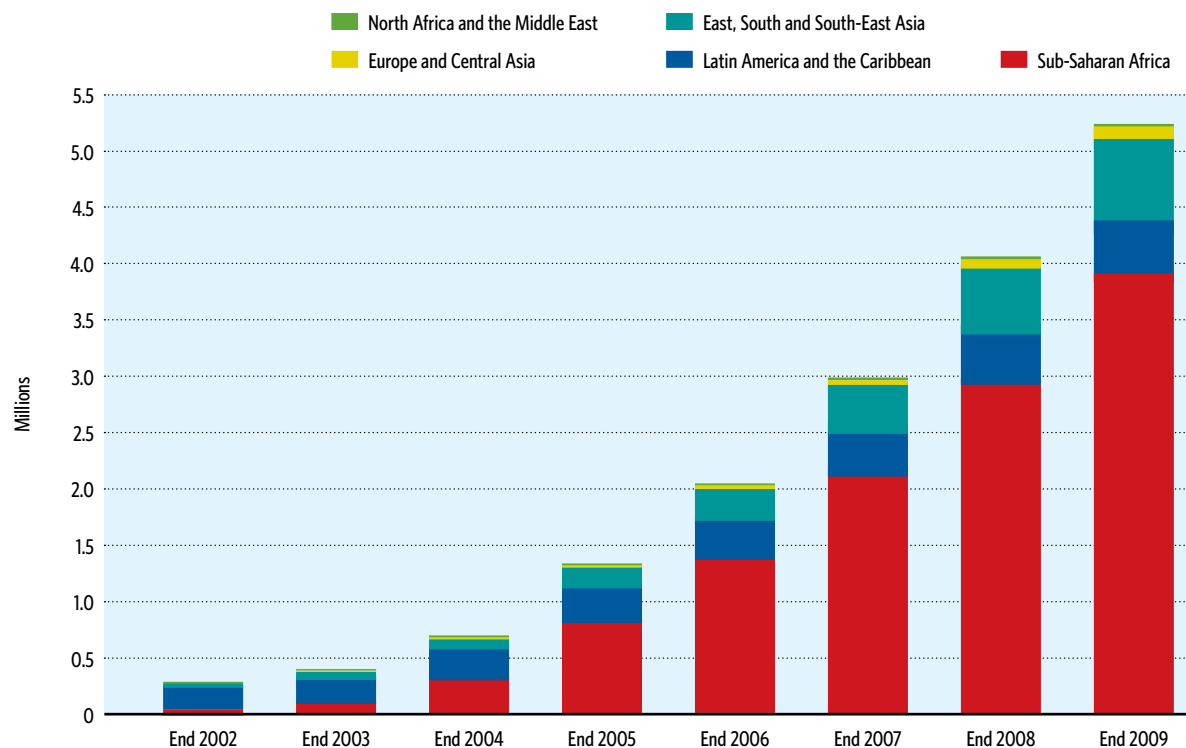
Geographical region	As of December 2009			As of December 2008		
	Number of people receiving antiretroviral therapy	Estimated number of people needing antiretroviral therapy, based on WHO 2010 guidelines [range] ^a	Antiretroviral therapy coverage, based on WHO 2010 guidelines [range] ^b	Number of people receiving antiretroviral therapy	Estimated number of people needing antiretroviral therapy, based on WHO 2010 guidelines [range] ^a	Antiretroviral therapy coverage, based on WHO 2010 guidelines [range] ^b
Sub-Saharan Africa	3 911 000	10 600 000 [9 700 000-11 500 000]	37% [34-40%]	2 950 000	10 400 000 [9 500 000-11 300 000]	28% [26-31%]
Eastern and Southern Africa	3 203 000	7 700 000 [7 200 000-8 300 000]	41% [38-45%]	2 416 000	7 600 000 [7 000 000-8 100 000]	32% [30-34%]
Western and Central Africa	709 000	2 900 000 [2 500 000-3 200 000]	25% [22-28%]	533 000	2 800 000 [2 500 000-3 200 000]	19% [17-22%]
Latin America and the Caribbean	478 000	950 000 [810 000-1 000 000]	50% [46-59%]	439 000	910 000 [790 000-1 000 000]	48% [44-56%]
Latin America	425 000	840 000 [700 000-940 000]	51% [45-61%]	400 000	810 000 [680 000-900 000]	49% [45-59%]
Caribbean	52 400	110 000 [95 000-120 000]	48% [42-55%]	39 900	110 000 [93 000-120 000]	37% [33-43%]
East, South and South-East Asia	739 000	2 400 000 [2 000 000-2 900 000]	31% [26-36%]	571 000	2 300 000 [2 000 000-2 900 000]	25% [20-29%]
Europe and Central Asia	114 000	610 000 [550 000-710 000]	19% [16-21%]	84 400	570 000 [510 000-660 000]	15% [13-17%]
North Africa and the Middle East	12 000	100 000 [88 000-120 000]	11% [10-14%]	9 100	91 000 [75 000-110 000]	10% [9-12%]
Total	5 254 000	14 600 000 [13 500 000-15 800 000]	36% [33-39%]	4 053 000	14 300 000 [13 200 000-15 400 000]	28% [26-31%]

Note: some numbers do not add up due to rounding.

a See Box 4.2 for further information on the methods for estimating the need for and coverage of antiretroviral therapy in 2008 and 2009.

b The coverage estimate is based on the unrounded estimated numbers of people receiving and needing antiretroviral therapy.

Fig. 4.1. Number of people receiving antiretroviral therapy in low- and middle-income countries, by region, 2002–2009



Twenty countries accounted for over 83% of the total number of patients receiving antiretroviral therapy in low- and middle-income countries in 2009, most of them in sub-Saharan Africa (Table 4.2). Home to the greatest absolute number of people living with HIV, South Africa now provides antiretroviral therapy to 18% of all patients treated worldwide. Zimbabwe recorded the highest increase in enrolment, where the number of people on treatment increased by almost 50% between December 2008 and December 2009. Despite continued progress, however, treatment in many of these countries remained well below the estimated needs (Table 4.2).

The number of people receiving antiretroviral therapy in high-income countries is at least 700 000, including about

385 000 in Europe and 300 000 in North America and the Caribbean, and 15 500 in Asia, Oceania and the Middle East. Worldwide, the total number of people accessing antiretroviral therapy in both low- and middle-income countries and high-income countries at the end of 2009 is estimated to be around 6 million.

The Global Fund to Fight AIDS, Tuberculosis and Malaria and the United States President's Emergency Plan for AIDS Relief (PEPFAR) remained the two major international sources of funding for antiretroviral therapy programmes in low- and middle-income countries in 2009. As of December 2009, Global Fund-supported programmes provided treatment to 2.5 million people, and programmes financed by PEPFAR supported antiretroviral therapy for 2.4 million people (8).

Box 4.2. Methods for estimating the need for and coverage of antiretroviral therapy among adults

Antiretroviral therapy coverage measures the proportion of people on antiretroviral therapy, as reported by national programmes, in relation to the estimated number of people in need of antiretroviral therapy. Therefore, figures used as denominators are estimates generated using a standardized statistical model (see below) based on, among other variables, the set of WHO-recommended criteria for antiretroviral therapy initiation (11). Considering the change in treatment guidelines adopted in 2010 (Box 4.1), coverage figures published in previous reports should not be compared to those reported herein.

Based on the recommendations of the UNAIDS Reference Group on Estimates, Modelling and Projections, UNAIDS and WHO have developed modelling methods and tools to generate country estimates of the magnitude of the epidemic and key impact indicators, including mortality (12). National HIV estimates are used as a basis to calculate the number of people in need. This includes all people who meet treatment initiation criteria, whether or not these people know their HIV status and their eligibility for antiretroviral therapy.

Treatment needs are influenced by a number of factors and are estimated using a software package called Spectrum (13). The tool takes into consideration the national epidemiological data and some key assumptions that include the adult HIV prevalence over time, the average survival of people living with HIV with and without antiretroviral therapy, and the average time between HIV seroconversion and eligibility for antiretroviral therapy. Country estimates of treatment need are the sum of the estimated need among adults and among children less than 15 years of age.¹

Country estimates of the need for antiretroviral treatment, and the corresponding regional and global estimates, are updated every two years based on the most recent epidemiological information and updated estimation methods.

Implications for global estimates of treatment and resource needs

WHO's recommendation to change the CD4 cell count threshold for initiation of antiretroviral therapy from 200 cells/mm³ to 350 cells/mm³ increased by 45% the number of people estimated to be in need of antiretroviral therapy in low- and middle-income countries in 2009, from 10.1 million to 14.6 million. While such an expansion in the number of eligible patients may increase the initial investments required to provide universal access to antiretroviral therapy in resource-limited settings, this expense is likely to be compensated for in the medium term by savings related to fewer hospitalizations, and lower morbidity and mortality rates. The effect of antiretroviral therapy on reducing HIV transmission may also improve the economic advantages of expanding access to antiretroviral therapy. A recent study estimated that, in South Africa, while adopting the revised criteria for treatment initiation would imply an immediate increase in investment needs, these would be fully offset by savings by 2014 and, over five years, overall programme costs would actually drop by about US\$ 470 million.²

While it is critical to implement the necessary expansions in programme capacity to incorporate the additional number of patients now eligible for treatment, it is also necessary to improve the approach to HIV treatment and care if the global response is to be sustained in the long run. The Treatment 2.0 Initiative, launched by WHO and UNAIDS, seeks to comprehensively maximize the value of antiretroviral therapy through the development of simpler, less resistance-prone combination treatment regimens, cheaper and simplified diagnostic tools, and a low-cost community-led approach to service delivery.

¹ For estimation methods regarding the number of children in need of antiretroviral therapy, see Box 5.6, Chapter 5.

² Kahn JG et al. Expanding ART for treatment and prevention of HIV in South Africa: estimated cost and cost-effectiveness 2011–2050 (unpublished data). Scenarios are based on an ART coverage rate of 90%.

Table 4.2. Number of people receiving antiretroviral therapy and percentage coverage in twenty low- and middle-income countries with the highest number of people receiving antiretroviral therapy in December 2009, progress between 2008 and 2009 in these countries

Country	Number of people receiving antiretroviral therapy in December 2008	Number of people receiving antiretroviral therapy in December 2009	Antiretroviral therapy coverage in 2009 [range] based on 2006 WHO guidelines	Antiretroviral therapy coverage in 2009 [range] based on 2010 WHO guidelines	Percentage increase, 2008-2009
South Africa	730 183	971 556	56% [48%-65%]	37% [35%-39%]	33%
Kenya	250 576	336 980	65% [55%-79%]	48% [42%-55%]	34%
India	234 581	320 074	41% [36%-46%]	26% [23%-28%]	36%
Nigeria	238 659	302 973	31% [25%-38%]	21% [18%-25%]	27%
Zambia	219 576	283 863	85% [72%->95%]	64% [56%-75%]	29%
Zimbabwe	148 144	218 589	49% [42%-57%]	34% [30%-38%]	48%
Thailand	185 086	216 118	76% [62%-95%]	61% [50%-78%]	17%
Uganda	153 718	200 413	53% [44%-67%]	39% [33%-46%]	30%
United Republic of Tanzania	154 468	199 413	44% [36%-53%]	30% [27%-34%]	29%
Malawi	147 497	198 846	63% [53%-77%]	46% [40%-53%]	35%
Brazil	194 984	... ^a	...[65%->95%] ^b	... [50%-89%] ^b	...
Ethiopia	132 379	176 632	... [58%-86%] ^b	... [45%-62%] ^b	33%
Mozambique	128 330	170 198	45% [36%-55%]	30% [26%-34%]	33%
Botswana	117 045	145 190	>95% [94%->95%]	83% [77%-97%]	24%
Rwanda	63 149	76 726	>95% [87%->95%]	88% [74%->95%]	21%
Cameroon	59 960	76 228	41% [34%-51%]	28% [25%-33%]	27%
Russian Federation	54 900	75 900	... [27%-42%] ^b	... [16%-24%] ^b	38%
Côte d'Ivoire	51 820	72 011	39% [33%-47%]	28% [24%-32%]	39%
Namibia	59 376	70 498	>95% [82%->95%]	76% [62%-92%]	19%
China	48 254	65 481	... [31%-67%] ^b	... [19%-38%] ^b	36%

a No 2009 data are available for Brazil.

b Estimates of the number of people needing antiretroviral therapy are currently being reviewed and will be adjusted, as appropriate, based on ongoing data collection and analysis. Therefore, coverage can only be presented as a range.

However, about 1.3 million people were receiving treatment through programmes jointly financed by the two initiatives; hence, together they supported programmes that provided treatment to approximately 3.7 million people at the end of 2009 (9,10).

Coverage of antiretroviral therapy in low- and middle-income countries continued to increase in 2009 and reached 36% [33-39%] of the 14.6 million [13.7 million-15.8 million] people estimated to be in need at the end of 2009 (Table 4.3). This revised estimate of total needs is based on the 2010 WHO guidelines for initiating antiretroviral therapy in patients with CD4 counts at or below 350 cells/mm³ (Boxes 4.1 and 4.2). In 2008, coverage under the same criteria was 28% [26-31%]. Although the trend remained clearly

positive, under the 2006 guidelines, global coverage would have reached 52% [47-58%] at the end of 2009.

As was the case in previous years, Latin America and the Caribbean (accounting for 6% of estimated treatment needs in low- and middle-income countries but for 9% of the total number of people receiving treatment) had an average coverage of 50% [46-59%], the highest regional level in 2009 (Table 4.1). This is due to the relatively longer duration of antiretroviral therapy programmes in some of the region's largest countries.

In sub-Saharan Africa, antiretroviral therapy coverage reached 37% [34-40%] in 2009. The region accounted for 72% of the estimated treatment need in low- and middle-

Table 4.3. Estimated percentage coverage with antiretroviral therapy in low- and middle-income countries by region, based on WHO 2010 and 2006 guidelines, December 2008 and December 2009^a

Geographical region	Antiretroviral therapy coverage, based on WHO guidelines 2010 (treatment initiation at CD4 count of <350 cells/mm ³), December 2009 [range] ^b	Antiretroviral therapy coverage, based on WHO guidelines 2006 (treatment initiation at CD4 count of <200 cells/mm ³), December 2009 [range] ^b	Antiretroviral therapy coverage, based on WHO guidelines 2010 (treatment initiation at CD4 count of <350 cells/mm ³), December 2008 [range] ^b	Antiretroviral therapy coverage, based on WHO guidelines 2006 (treatment initiation at CD4 count of <200 cells/mm ³), December 2008 [range] ^b
Sub-Saharan Africa	37% (34%-40%)	53% (47%-61%)	28% (26%-31%)	42% (37%-48%)
Eastern and Southern Africa	41% (38%-45%)	59% (53%-67%)	32% (30%-34%)	47% (42%-53%)
Western and Central Africa	25% (22%-28%)	36% (30%-44%)	19% (17%-22%)	28% (23%-35%)
Latin America and the Caribbean	50% (46%-59%)	67% (61%-78%)	48% (44%-56%)	65% (60%-76%)
Latin America	51% (45%-61%)	67% (61%-79%)	49% (45%-59%)	66% (61%-78%)
Caribbean	48% (42%-55%)	67% (58%-80%)	37% (33%-43%)	54% (46%-65%)
East, South and South-East Asia	31% (26%-36%)	47% (39%-56%)	25% (20%-29%)	38% (31%-46%)
Europe and Central Asia	19% (16%-21%)	31% (26%-36%)	15% (13%-17%)	25% (21%-30%)
North Africa and the Middle East	11% (10%-14%)	18% (15%-23%)	10% (9%-12%)	16% (13%-21%)
Total	36% (33%-39%)	52% (47%-58%)	28% (26%-31%)	42% (38%-48%)

a For an explanation of the methods used, see the explanatory notes for Annex 1 and Box 4.2.
 b The coverage estimate is based on the unrounded numbers of people receiving and needing antiretroviral therapy.

Table 4.4. Low- and middle-income countries with an estimated ART coverage of 50-80% and 80% or higher as of December 2009^a

Countries with 50-80% antiretroviral therapy coverage (n = 21)	Countries with 80% or higher antiretroviral therapy coverage (n = 8)
Argentina	Botswana
Benin	Cambodia
Brazil	Croatia ^b
Chile	Cuba
Costa Rica	Guyana
El Salvador	Oman ^b
Ethiopia	Romania
Georgia ^b	Rwanda
Lao People's Democratic Republic	
Mali	
Mexico	
Namibia	
Papua New Guinea	
Senegal	
Slovakia ^b	
Suriname	
Swaziland	
Thailand	
Tunisia ^b	
Turkey	
Zambia	

a Coverage estimates are calculated based on the new 2010 WHO guidelines of treatment initiation at a CD4 count < 350 cells/mm³.
 b Countries with an estimated antiretroviral therapy need of less than 1000 people. Data for these countries should be interpreted cautiously due to the impact of ranges of uncertainty around these estimates on coverage.

income countries, and 74% of the total number of people receiving treatment at the end of 2009. However, important intraregional differences in coverage were observed: whereas 41% [38-45%] of those in need had access to antiretroviral therapy in Eastern and Southern Africa, in

West and Central Africa antiretroviral therapy coverage stood at 25% [22-28%]. The lower coverage level observed in Western and Central Africa is partially explained by the fact that Nigeria, while accounting for 50% of the treatment need in the subregion, had an estimated coverage of 21%, thus affecting the group estimate.

Coverage in 2009 improved across all the other regions as well, but was lowest in East, South and South-East Asia with 31% [26-36%], Eastern Europe and Central Asia, with 19% [16-21%], and North Africa and the Middle East, where only 11% [10-14%] of the regional antiretroviral therapy needs were met. In these regions, a number of countries face HIV epidemics that are concentrated among harder-to-reach and most-at-risk populations who, in addition to having only limited access to treatment and care services, face programmes predominantly oriented towards the needs of the general population.

Based on WHO's 2010 treatment guidelines, at the end of 2009, eight low- and middle-income countries (Botswana, Cambodia, Croatia, Cuba, Guyana, Oman, Romania, Rwanda) had already achieved universal access to antiretroviral treatment, commonly understood as providing antiretroviral treatment to at least 80% of patients in need (Table 4.4). Twenty-one other countries had coverage rates higher than 50%. Under previous CD4 count criteria for antiretroviral therapy initiation (2006 WHO guidelines), nine other countries would have also reached universal access to antiretroviral therapy in 2009 (Argentina, Chile, Costa

Rica, Georgia, Lao People's Democratic Republic, Namibia, Swaziland, Turkey and Zambia).

4.1.2. Access to antiretroviral therapy among women and children

A total of 143 countries reported data disaggregated for adults and children. About 356 400 children less than 15 years of age were receiving antiretroviral therapy at the end of 2009, up from 275 300 at the end of 2008, or a 29% year-on-year increase (Chapter 5 provides an in-depth analysis on paediatric treatment). Children represented 6.8% of people receiving antiretroviral therapy and 8.7% of people in need.

Overall antiretroviral therapy coverage among children was lower than among adults in low- and middle-income countries. Of the 1 270 000 [830 000-1 700 000] children estimated to be in need of antiretroviral therapy, only 28% [21-43%] had access to treatment, versus 37% of adults adults [35-41%]. This is due to the fact that sub-Saharan

Africa accounts for 89% of paediatric needs but has an estimated coverage rate of 26% (Table 4.5). Indeed, in Latin America and the Caribbean, East, South and South-East Asia, and in Eastern Europe and Central Asia, coverage among children is higher than among adults.

Data disaggregated by sex on the number of people receiving and needing antiretroviral therapy are available from 95 low- and middle-income countries, representing 88% of the 5.25 million people receiving treatment in 2009.¹ Women represented 58% of people on antiretroviral therapy and 53% of those in need. Overall, antiretroviral therapy coverage was higher among women, estimated at 39%, compared with 31% among men. However, this pattern was not observed in all regions (Table 4.6).

¹ Some countries provided disaggregated data only for a proportion of all people receiving antiretroviral therapy in the country. For those countries with incomplete datasets, treatment data by sex were obtained by applying male/female ratios from existing data to the numbers of people on treatment. Similarly, for 15 countries that were able to supply data by sex in 2008 but not in 2009, available male/female ratios from 2008 were applied to 2009 data.

Table 4.5. Number of children less than 15 years receiving and estimated to need antiretroviral therapy, and percentage coverage among children and adults in low- and middle-income countries,^a by region, December 2009

Geographical region	Number of children (0-14 years) receiving antiretroviral therapy, December 2009	Estimated number of children needing antiretroviral therapy, 2009 [range] ^b	Antiretroviral therapy coverage among children, December 2009 [range] ^c	Antiretroviral therapy coverage among adults, December 2009 [range] ^b
Sub-Saharan Africa	296 000	1 140 000 [710 000-1 500 000]	26% [19-42%]	38% [36-42%]
Eastern and Southern Africa	254 900	790 000 [530 000-1 000 000]	32% [25-48%]	42% [40-46%]
Western and Central Africa	41 000	350 000 [180 000- 510 000]	12% [8-22%]	27% [25-30%]
Latin America and the Caribbean	18 600	32 200 [23 000-42 000]	58% [45-80%]	50% [46-67%]
Latin America	16 300	24 100 [19 000-31 000]	68% [52-87%]	50% [45-69%]
Caribbean	2 400	8 100 [4 100-12 000]	29% [19-57%]	50% [45-59%]
East, South and South-East Asia	36 500	83 400 [61 000-140 000]	44% [27-59%]	30% [26-36%]
Europe and Central Asia	4 800	9 700 [5 700-15 000]	49% [31-58%]	18% [16-21%]
North Africa and the Middle East	560	10 000 [5 200-15 000]	6% [4-11%]	12% [11-16%]
Total	356 400	1 270 000 [830 000-1 700 000]	28% [21-43%]	37% [35-41%]

Note: some numbers do not add up due to rounding.

a For an explanation of the methods used, see the explanatory notes for Annex 1 and Box 4.2.

b The coverage estimate is based on the unrounded numbers of people receiving and needing antiretroviral therapy.

c Based on 2010 WHO guidelines of treatment initiation at a CD4 count of <350 cells/mm³.

Table 4.6. Comparison of number of men and women receiving and estimated to need antiretroviral therapy and percentage coverage, by region, December 2009^a

Geographical region	Men			Women		
	Coverage ^b	Number receiving ART	Number in need	Coverage ^b	Number receiving ART	Number in need
Sub-Saharan Africa	32%	1 353 200	4 200 000	40%	2 321 000	5 800 000
Eastern and Southern Africa	37%	1 120 800	3 000 000	44%	1 882 000	4 200 000
Western and Central Africa	20%	232 400	1 100 000	29%	439 000	1 500 000
Latin America and the Caribbean	49%	276 200	570 000	55%	163 000	300 000
Latin America	49%	261 300	540 000	57%	147 000	260 000
Caribbean	55%	14 900	27 000	45%	16 000	36 000
East, South and South-East Asia	22%	284 300	1 300 000	28%	191 400	690 000
Europe and Central Asia	16%	20 600	130 000	16%	15 000	97 000
North Africa and the Middle East	11%	5 000	47 000	9%	4 300	50 000
Total	31%	1 940 000	6 200 000	39%	2 690 000	6 900 000

a Based on 95 countries reporting disaggregated data by sex.

b The coverage estimate is based on the unrounded numbers of people receiving and needing antiretroviral therapy.

Box 4.3. Uninterrupted supplies of drugs for antiretroviral therapy: a major challenge for accessibility to and retention on antiretroviral therapy

Drug stock-outs remain an issue of concern in low- and middle-income countries. The proportion of countries experiencing stock-outs of drugs for antiretroviral therapy remained stable in 2009 vis-à-vis previous years. Of the 94 countries reporting information this year, 36 (38%) reported at least one or more stock-out of antiretroviral drugs in health facilities in 2009, compared to 31 out of 90 countries (34%) in 2008 and 25 out of 66 countries (38%) in 2007.

Ensuring an uninterrupted supply of antiretroviral drugs is critical to minimize the emergence of HIV drug resistance, protect the health and well-being of patients, and ultimately reach universal access goals. As such, greater efforts must be made to identify and address bottlenecks in drug procurement and management, particularly in the context of an expected increase both in the number of people on treatment and complexity of drug regimens, as more patients move from first- to second- and third-line antiretroviral regimens. Robust and up-to-date information systems are a critical element in this regard, as only rigorous pharmacy monitoring at the site level allows stocks to be adequately managed. Equally relevant is the proper documentation and follow up of patient cohorts over time, thus reinforcing monitoring of the antiretroviral therapy programme.

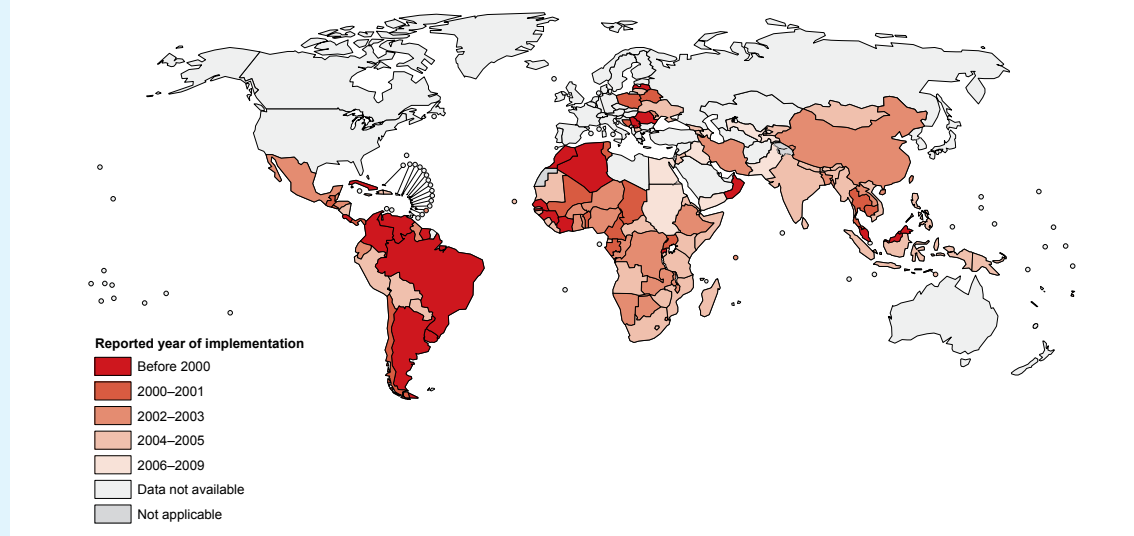
Improved partner coordination at the country level under strong governmental leadership is key to ensure the responsiveness and integrity of supply systems for antiretroviral drugs. Once potential stock-outs are identified, governments and other implementing partners, through close collaboration and information sharing, must assess district or province stock levels and reallocate them as needed. In Rwanda, the Coordinated Procurement and Distribution System for antiretrovirals and drugs for opportunistic infections brings together government officials, donors, national institutions and international organizations. It has succeeded in reducing stock-outs and drug expiry by ensuring that, once potential antiretroviral stock-outs are identified, a partner can step in and fill any gaps as needed. When the stock-out is a national issue and concerns all districts, an internationally agreed approach is to place an emergency order from partners who have buffer stocks in their warehouses at regional (Johannesburg, Nairobi, Accra) or headquarter levels and explore which options would respond more rapidly to the urgent country need.

Box 4.4. Maturity of national antiretroviral therapy programmes

A total of 118 low- and middle-income countries provided data on the year of launch of national antiretroviral therapy programmes.¹ In 81% of cases, antiretroviral therapy programmes have been in place for more than five years. This figure includes a subgroup of 22 countries where antiretroviral therapy programmes were introduced more than 10 years ago.

A regional breakdown reveals that in Latin America and the Caribbean, 96% of reporting countries have antiretroviral therapy programmes that have been in place for at least five years. The corresponding figures are 89% in sub-Saharan Africa, 71% in East and South-East Asia, 56% in North Africa and the Middle East, and 65% in Eastern Europe and Central Asia. Among those countries with the highest burden of HIV, programmes have been in place for at least five years in Nigeria (year of initiation: 2002), Ethiopia (2003), Zambia (2003), India (2004), Kenya (2004) and South Africa (2004).

Fig. 4.2 Starting year of implementation of antiretroviral therapy programmes in low- and middle-income countries, by country



¹ Data on the starting year of implementation of antiretroviral therapy programmes in low- and middle income countries were obtained from the reporting form of the universal access report, relevant country websites and regional offices.

4.1.3. Availability of antiretroviral therapy

The number and distribution of health facilities providing antiretroviral therapy are important indicators of the scale-up of and access to treatment services. In 2009, 116 low- and middle-income countries reported a total of 18 600 health facilities providing antiretroviral therapy. Of these facilities, 80% were in the public sector and 11% in the private sector (9% were unspecified).

Ninety-nine countries provided data for both 2008 and 2009. In these countries, the reported number of health facilities providing antiretroviral therapy increased from 11 833 to 16 134, or a 36% increase in one year. It increased by 26% in sub-Saharan Africa (from 5778 to 7302 in 39 countries); 5% in Latin America and the Caribbean (from 1847 to 1948 in 17 countries); 64% in East, South and South-East Asia (from 3660 to 6013 in 20 countries) and 69% in Eastern Europe and Central Asia (from 458 to 776 in 16 countries). In North Africa and the Middle East, the number of facilities providing antiretroviral therapy went up from 90

in 2008 to 95 in 2009 across seven reporting countries, an increase of 6%.

The average number of people receiving antiretroviral therapy per health facility increased from 260 in 2008 to 274 in 2009. Health facilities in sub-Saharan Africa continue to treat more people per site than in the rest of the world, with an average of 452 people per health facility providing antiretroviral therapy versus 157 in Latin America and the Caribbean, 123 in East, South and South-East Asia, 33 in Eastern Europe and Central Asia, and 63 in North Africa and the Middle East.

4.1.4. Outcomes and impact of scaling up antiretroviral therapy

4.1.4a. Outcomes at the programme level: retention on antiretroviral therapy

Antiretroviral therapy is a lifelong intervention. As such, it requires a robust framework to adequately monitor and

Table 4.7. Number of countries reporting on retention on antiretroviral therapy among 149 low- and middle- income countries, 2008 and 2009

	2008		2009	
	Number of countries reporting	Number of patients assessed	Number of countries reporting	Number of patients assessed
Retention at 12 months	61	297 408	115	519 890
Retention at 24 months	42	132 427	66	284 017
Retention at 36 months	30	52 572	56	184 679
Retention at 48 months	22	25 643	46	106 696

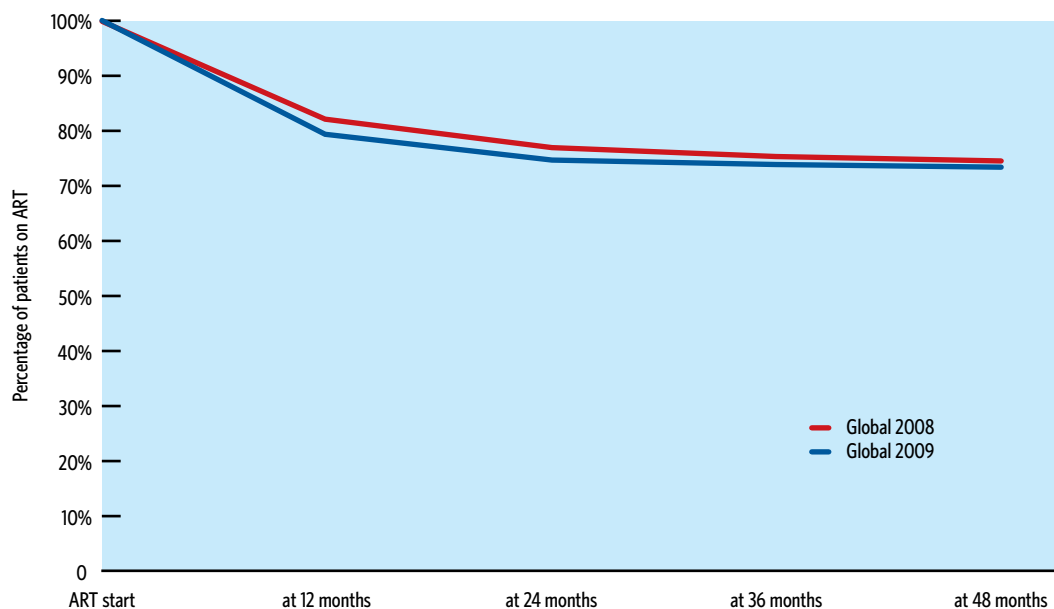
evaluate processes, outcomes and long-term impact, both at the individual and at the population level. Measuring patient retention, or the percentage of adults and children with HIV who continue to receive treatment after initiating antiretroviral therapy (excluding patients who died, were lost to follow up or stopped treatment among those who had started), provides programme managers with critical information to monitor systemic progress, identify bottlenecks and implement timely programmatic changes whenever necessary.

Countries have continued to improve the monitoring and reporting of programme retention on antiretroviral therapy. As summarized in Table 4.7, the rate of reporting for the

Box 4.5. Retention of patients on antiretroviral therapy: tracking trends at the global level, 2008 and 2009

For each time-point (12, 24, 36 and 48 months), countries were requested to report the number of patients initiated on antiretroviral therapy and still on treatment (the numerator) as well as the total number of patients initiated on antiretroviral therapy during each period (the denominator). For each time-point, numerators and denominators were then aggregated to produce global estimates. Figure 4.3 shows these estimates for 2008 and 2009. While a direct comparison of retention levels between the two years may not be appropriate, as reporting periods are not always clearly specified and reported data may not reflect the most recent available information, trends detected in 2009 are clearly consistent with those observed in 2008 – a fact that is especially relevant given the increase in the number of reporting countries and patients assessed.

Fig. 4.3. Retention on antiretroviral therapy up to 48 months, 2008 and 2009



While progress has been made in documenting retention on antiretroviral therapy over time across countries and regions, this is an area where numerous challenges remain to be addressed (15). Many programmes are still technically and operationally unable to provide retention data, especially for longer periods. Retention rates may be overestimated when calculated exclusively on survival information, without taking into account patients lost to follow up or those stopping treatment, while improper record-keeping of patients transferred out to another clinic may underestimate true rates. Also, when reported, country data may not be representative of the full programme when derived from a non-random selection of sites. Indeed, reporting programmes and sites are likely to be better organized and may exhibit stronger performance than those not providing any information, further affecting the representativeness of reported figures. Finally, reported data may not exactly reflect outcomes in 2009 but cumulative outcomes or outcomes during a previous period. All these factors may contribute to the important variation in reported results across countries.

indicators on retention on antiretroviral therapy almost doubled both in terms of the number of countries reporting and the number of patients assessed for outcomes.

Among 47 countries in sub-Saharan Africa, 37, 23, 20 and 15 countries reported retention rates on antiretroviral therapy at 12, 24, 36 and 48 months, respectively.

Reported data for each time-point were aggregated to produce global estimates. Data on the proportion of patients retained on antiretroviral therapy over time continue to show that most patient attrition – or discontinuation of antiretroviral therapy – occurs within the first year and that retention rates tend to stabilize thereafter. In 2009, the average global retention rate at 12 months was 82.0% (interquartile range: 77–93%). It dropped to 76.9% (interquartile range: 70–87%) at 24 months and remained stable at 75% (interquartile range: 63–81%) and 74.5% (interquartile range: 57–82%) at 36 and 48 months, respectively. Interquartile ranges showed the important variation in reported retention rates across countries (Box 4.5).

These figures are consistent with those from an updated meta-analysis of 39 cohorts from sub-Saharan Africa (14). Retention was estimated at between 70% and 77% at 24 months, and 65–72% at 36 months. The authors noticed that the rate of retention at 24 months was higher than their previous estimate. Such an improved performance could reflect a change in the criteria for initiation of antiretroviral therapy, as higher CD4 cell counts at enrolment have been associated with lower mortality and improved treatment outcomes.

A total of 61 countries reported disaggregated retention data at 12 months by sex and 53 countries provided similarly disaggregated data by age (children younger than 15 years and adolescents/adults older than 15 years). Globally, retention at 12 months was found to be almost the same among women and men, averaging 81% and 82%, respectively. Among children, average retention rates, at 73%, were slightly lower than among adolescents/adults, which stood at 82%.

Whereas it is critical to improve retention on antiretroviral therapy and long-term programmatic performance (16), more attention must be devoted to the attrition of patients in HIV care before initiation of antiretroviral therapy and how it may negatively affect the performance of antiretroviral therapy programmes. Patients who tested HIV-positive and enrolled in HIV care may not all start antiretroviral therapy or, more worryingly, may start late after reaching eligibility levels. Among 44 844 patients enrolled in care between May 2004 and December 2007 in South Africa, 22 083 were or became eligible for antiretroviral therapy. However, while 68% of them were receiving antiretrovirals after two years,

26% had died before starting treatment and 6% were alive and untreated. The delay between eligibility for and start of antiretroviral therapy was reduced from a median of 122 days in 2004 to 78 days in 2007.¹ A few similar studies are available but all showed confluent results, calling for a need to better understand and reduce pre-antiretroviral therapy attrition and mortality (17–20).

As monitoring systems and cohort studies typically focus on outcomes in patients who are known to have started treatment, this “unseen mortality”¹ often remains unreported or underreported. It is critical to step up efforts to better manage waiting lists and closely monitor any delays in initiation of antiretroviral therapy once a patient is deemed eligible, particularly as guidelines worldwide adopt a higher CD4 cell count criterion for initiation of antiretroviral therapy.

4.1.4b. Impact of antiretroviral therapy programmes

The magnitude of the toll the epidemic exacts on people and societies is such that appropriately measuring and understanding how HIV care and treatment impact on population mortality is crucial. In addition, as programmes mature, monitoring their impact on mortality, morbidity and quality of life is equally essential to evaluate overall programme effectiveness and efficiency, key elements to ensure the continued political commitment necessary to sustain a lifelong intervention.

Issues related to the absence of or delay in the generation of vital statistics in many low- and middle-income countries explain most of the current difficulties in assessing the impact of antiretroviral therapy on mortality at the population level. Vital or civil registration systems are weak in many low- and middle-income countries, especially in countries with a high HIV burden, rendering the appropriate measurement of AIDS-related mortality particularly challenging. While few comprehensive studies are available on the matter, a systematic analysis of worldwide mortality among adults aged 15–59 years from 1970 to 2010 showed that mortality increased substantially in sub-Saharan Africa starting in the late 1980s (in fact, it more than doubled in the southern region) and began to decline since 2005, a trend that coincides with an increase in access to antiretroviral treatment (21,22). In South Africa, a recent study based on demographic surveillance data in KwaZulu Natal correlated the decline in mortality in the region, particularly among young adults, with the decline in HIV-related mortality (Box 4.6). Moreover, there is a growing body of scientific evidence that points to the important role antiretroviral therapy can play in the prevention of HIV transmission (Box 4.7).

¹ Outcomes in patients waiting for antiretroviral treatment in the Free State Province, South Africa: prospective linkage study. (Ingile S et al., personal communication, 2010).

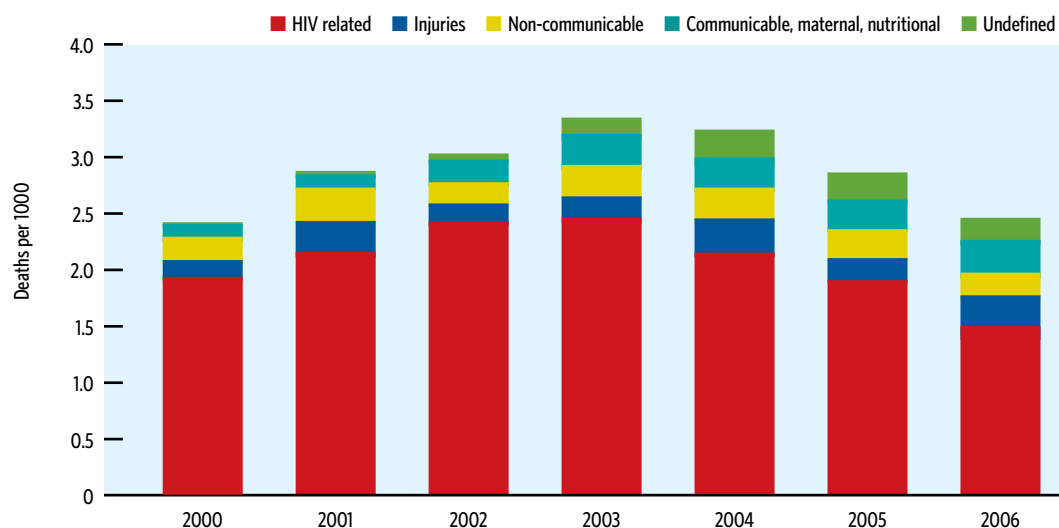
Box 4.6. Reduction in AIDS-related mortality in KwaZulu Natal, South Africa

WHO and UNAIDS have launched a series of country consultations to better assess the impact of antiretroviral therapy programmes, in particular, on population mortality. In South Africa, it was conducted in partnership with StatsSA (Statistics South Africa) and the national Department of Health. The best available data are identified with a special emphasis on identifying group-level correlations between mortality and antiretroviral therapy programme data. However, causes of death are often inaccurately recorded and trends in mortality can seldom be directly correlated with changes in AIDS-related mortality.

In KwaZulu Natal, provincial statistics showed an increase in mortality up to 2003 and a stabilization thereafter, which coincided with the introduction and roll-out of the antiretroviral therapy programme. These trends in mortality were particularly marked in the 25–34 years' age group.¹

A demographic surveillance programme in the district of Umbkhanyakude in KwaZulu Natal correlated the decline in mortality in the age group of 25–49 years with the decline in HIV-related mortality. Verbal autopsies were conducted for all 7930 deaths observed between 2000 and 2006. The reduction in HIV-related mortality was estimated at 22% in men and 29% in women between 2002–03 and 2005–06 (28).

Fig. 4.4. Cause-specific standardized mortality ratios for adults aged 25–49 years, KwaZulu-Natal, South Africa, 2000–2006



Source: Herbst et al. (28)

While research on the impact of scale-up of antiretroviral therapy on population mortality is still limited, it is expected that more data will become available as programmes mature and demographic surveillance and HIV cohort monitoring systems are better integrated.

¹ Collaborative project StatSA, DoH, UNAIDS, WHO – preliminary analysis (Stoneburner R, personal communication, 2010).

Box 4.7. Impact of antiretroviral therapy on HIV prevention

As the strongest predictor of HIV transmission risk in epidemiologic studies is the level of HIV in blood, a significant drop in the amount of virus is essential to interrupt or drastically reduce transmission. Indeed, research has shown that viral load predicts the risk of sexual transmission of HIV-1, and that transmission from persons with levels of less than 1500 copies of HIV-1 RNA per millilitre is rare (29). A 2009 meta-analysis that included 11 cohorts (5021 heterosexual couples) found only a minimal risk of sexual transmission while on antiretroviral therapy for HIV-1 concentrations less than 400 copies/ml (30). A recent randomized controlled study of genital herpes simplex virus treatment among long-term, HIV-serodiscordant heterosexual couples in Africa found a 92% reduction in transmission if the HIV-positive partner was on antiretroviral therapy. Prevention of maternal-to-child transmission offers further proof of concept that antiretroviral therapy interrupts HIV transmission. There is also growing evidence of the impact of antiretroviral therapy on community-level HIV transmission. In British Columbia, a decrease in community plasma HIV RNA concentrations and HIV incidence among injecting drug users was associated with antiretroviral therapy use (32). In San Francisco, between 2004 and 2008, ecological correlations show that the number of HIV diagnoses fell by 45%, the average viral load among the HIV-positive population by 40%, and actual HIV incidence by one third between 2006 and 2008 (33,34).

Theoretical models have been used as well to estimate the impact of antiretroviral therapy on the incidence of and mortality from HIV. A model published in 2008 focused on a generalized HIV epidemic setting largely driven by heterosexual sex. Using data from Malawi, South Africa, Uganda and elsewhere, the model showed a 95% reduction in HIV incidence over 10 years with a strategy that combined universal voluntary HIV testing and counselling followed by immediate enrolment in antiretroviral therapy of all people who tested positive (12). It was premised on earlier analyses suggesting that rapid scale-up of conventional antiretroviral therapy approaches could meaningfully reduce mortality (35) and have a considerable impact on HIV incidence (36,37). The potential impact of such a “test and treat” strategy has also been modelled for Washington, D.C., where it could potentially decrease the number of new HIV infections by as much as 26% over ten years (38). The implementation of a similar approach in San Francisco could cut the number of new infections by 91% (39). Among the factors to consider in “test and treat” approaches are the risk of HIV drug resistance (see section 4.1.6), the need to maximize adherence, how to adequately deal with the acute phase of HIV infection and the need to develop strategies to address a potential increase in sexual risk-taking integrating the values and principles of Positive Health, Dignity and Prevention into the various policy and programmatic elements of the HIV/AIDS response (see Box 3.11).

WHO convened two international consultations in November 2009 to clarify research priorities, explore feasibility and acceptability issues, and review the human rights and ethical considerations of expanding antiretroviral therapy for prevention purposes. The consultations involved a wide array of specialists, including researchers, clinicians, prevention experts, human rights specialists, ethicists, organizations of people living with HIV, national programme managers and community groups.¹ WHO and partners are currently engaged with stakeholders on further analysis of the impact of antiretroviral therapy on tuberculosis (TB), the relative importance of drug resistance and other assumptions, the effect of combining pre-exposure prophylaxis and “test and treat” approaches, the impact on prevention of mother-to-child transmission and an in-depth examination of the costs and benefits of expanding access to antiretroviral therapy. WHO will work with key stakeholders to help set the research agenda and to periodically review the evidence as it becomes available.

¹ The presentations, list of participants and outcomes of the meetings are available at <http://www.who.int/hiv/events/artprevention/>.

In addition to the impact of antiretroviral therapy programmes on mortality and HIV transmission, investing in the scale-up of antiretroviral therapy has also tangibly benefited other health services and access to care in general in multiple ways. Indeed, the impact of antiretroviral therapy on reducing morbidity and use of hospital services has been documented in high-income countries (23). Antiretroviral therapy has been associated with a reduction in the burden of care placed on often overwhelmed health systems, particularly on inpatient care services, and with a decrease in mortality among health workers in countries highly affected by the epidemic (24). There is evidence as well that capacity put in place to enable the roll-out of antiretroviral therapy programmes, such as drug supply management, has had a broader positive impact on other health services (25–27).

4.1.5. Prevention and assessment of HIV drug resistance

As access to antiretroviral therapy continues to expand, the emergence of HIV drug resistance is inevitable due to HIV’s high mutation rate, viral recombination, and the need for sustained, lifelong treatment. Because HIV drug resistance has the potential to undermine the dramatic gains that antiretroviral therapy has had in reducing the morbidity and mortality among HIV-positive patients, it is necessary to monitor HIV drug resistance and factors related to its evolution. Treatment programmes should also be adjusted, if necessary, to maintain the effectiveness of first- and second-line regimens.

HIV drug resistance may be acquired or transmitted. A recent review of studies conducted in sub-Saharan Africa

Box 4.8. Establishing an HIV drug resistance early warning system in Namibia

Based on 2008 antenatal serosurveillance data, an estimated 17.8% of Namibians aged 15–49 years are infected with HIV-1 (42). The epidemic is predominantly spread via heterosexual contact, and prevalence estimates vary by region, with up to 31% infected with HIV-1 in the most heavily affected areas in the north (43). In December 2009, 70 500 patients were reported to be on antiretroviral therapy, a coverage estimated at 76% based on WHO 2010 guidelines.

In 2009, Namibia's Ministry of Health and Social Services implemented an early warning system to monitor HIV drug resistance (44,45). Five indicators were selected: (i) antiretroviral therapy prescribing practices, (ii) patients lost to follow up at 12 months, (iii) patient retention on a first-line antiretroviral therapy regimen at 12 months, (iv) on-time antiretroviral drug pick-up, and (v) continuity of antiretroviral drug supply. An assessment of the available medical and pharmacy records demonstrated that existing record-keeping methods supported the monitoring of only three of the initial five selected indicators. Monitoring of the three indicators was then piloted in nine antiretroviral therapy sites. Results revealed that most sites achieved the targets and levels deemed appropriate for each indicator: 100% of patients were initiated on appropriate first-line antiretroviral therapy regimens across all nine sites; eight sites maintained the proportion of patients lost to follow up at under 20% 12 months after treatment initiation, and six sites had 0% of patients switched to a second-line regimen within the first 12 months of antiretroviral therapy (in the remaining three sites the proportion was less than 1%). The pilot uncovered, however, that although the overall proportion of patients lost to follow up at 12 months met recommended targets, 20.8% of patients had a mean treatment interruption of 2.3 months within the first 12 months of treatment, placing them at increased risk for treatment failure and development of HIV drug resistance.¹ The initial implementation of the early warning system uncovered the need to further strengthen antiretroviral therapy record systems to enable the eventual monitoring of all five selected indicators in subsequent years. The results also highlighted the need to reinforce defaulter tracking mechanisms to enhance long-term patient retention, optimize the quality of patient care and minimize drug resistance.

¹ Inadequate systems to trace patient transfers to other antiretroviral therapy sites may cause treatment interruption rates to be overestimated.

and India found, as expected, a high frequency of resistance mutations among patients failing first-line therapy and with detectable viral loads, ranging from 47% to 93% for non-nucleoside reverse transcriptase inhibitors (NNRTIs) and from 32% to 60% for thymidine analog nucleoside reverse transcriptase inhibitors (NRTIs) (40). On the other hand, most reports from low- and middle-income countries have described low rates of transmitted resistance. Studies conducted in Africa found NNRTI resistance rates between 0% and 5.6% and NRTI resistance rates between 0% and 3.7%. Transmitted protease inhibitor mutations were rare (41). However, considerable variations in study designs, including a range of sample sizes, drug regimens, previous exposure to antiretroviral drugs and duration of follow-up, limit the comparability of these study results.

To improve surveillance of HIV drug resistance with standardized approaches, WHO, in collaboration with HIVResNet, an international network of experts, countries and institutions, have developed a global strategy for the prevention and assessment of HIV drug resistance. WHO recommends that countries develop a national strategy for the prevention and assessment of HIV drug resistance based on three key assessments: (1) routine monitoring of HIV drug resistance "early warning indicators", (2) surveys to monitor the emergence of HIV drug resistance and related programmatic factors in populations receiving antiretroviral therapy, and (3) surveys to assess transmitted HIV drug resistance in recently infected populations. As of mid-2010, over 60 countries had implemented one or more elements of the HIV drug resistance prevention and assessment strategy. To facilitate implementation of country plans,

WHO supports the accreditation of national, regional and specialized HIV drug resistance testing laboratories; as of December 2009, 24 HIV drug resistance testing laboratories had been accredited.

4.1.5a. HIV drug resistance – early warning indicators

Research shows that various programme and site factors are closely associated with the emergence of HIV drug resistance, and their proper monitoring can serve as early warning indicators to support appropriate programme management. WHO has developed six core and two optional early warning indicators, each with an associated target, and recommends their annual monitoring in all or a large number of representative sites.

As of December 2009, 45 countries had implemented early warning indicators, up from 14 in 2008.

4.1.5b. Surveys to monitor the emergence of HIV drug resistance and associated programmatic factors in populations

Standardized surveys, performed at sentinel sites providing adult or paediatric antiretroviral therapy, are also important instruments to assess the emergence and prevention of HIV drug resistance in populations receiving first-line antiretroviral therapy (6). Surveys to monitor HIV drug resistance identify factors that can be addressed by making adjustments at the site or programme level to minimize the emergence of preventable drug resistance. Performed regularly at representative sites, the surveys are designed to be integrated easily into countries' routine HIV-related monitoring and evaluation activities, and can substantially

Box 4.9. Using sentinel surveys to monitor the emergence of HIV drug resistance in Burundi

Between 2002 and 2009, the number of patients receiving antiretroviral therapy in Burundi increased from 600 to 17 661. In 2007 and 2008, Burundi conducted a survey to monitor the prevention and emergence of HIV drug resistance and associated programme factors, following the WHO generic protocol (46) at two large urban antiretroviral therapy sites in Bujumbura. In total, 121 and 129 adult patients consecutively initiating first-line antiretroviral therapy were enrolled at each site, respectively. Following WHO's protocol, it is recommended that at least 70% of patients should achieve HIV drug resistance prevention (as defined by viral load suppression of less than 1000 copies/ml) 12 months after initiation of antiretroviral therapy. At site A, 83.6% achieved prevention of HIV drug resistance, and of those with detectable virus, HIV drug resistance was detected in 3%. At site B, 81% achieved prevention of HIV drug resistance; of those with detectable virus, HIV drug resistance was detected in 5%. Importantly, at each site, 13% and 14% of patients, respectively, were classified as having "possible HIV drug resistance" because they had been lost to follow up, had stopped antiretroviral therapy before 12 months or had had a detectable viral load 12 months after the start of therapy. Survey results suggest the need to reinforce programmes to support adherence to antiretroviral therapy as well as tracking systems to minimize the number of patients lost to follow up.

strengthen their evidence base for optimal selection of national antiretroviral therapy regimens. As of December 2009, 15 countries had implemented surveys to monitor the emergence of HIV drug resistance and associated programme factors in one or more sites, up from six countries in 2008.

4.1.5c. Surveys to assess transmitted HIV drug resistance

The WHO HIV drug resistance threshold survey methodology was developed for the surveillance of transmitted HIV drug resistance in resource-limited settings (47,48). As transmitted drug-resistant HIV is expected to develop first in cities or health districts where antiretroviral therapy has been widely available for several years, WHO recommends that countries prioritize these areas when rolling out activities for surveillance of resistance. The methodology's eligibility criteria for selecting sites and individuals have been designed to minimize the inclusion of antiretroviral therapy-experienced individuals and/or chronically infected individuals, and defines three categories for transmitted HIV drug resistance: low (level less than 5%), moderate (between 5 and 15%) and high (more than 15%). The results of these surveys, combined with results from other key assessments, provide critical information relevant to prevention of and planning for antiretroviral therapy and drug resistance. At the end of 2009, 29 countries had implemented surveys to assess transmitted HIV drug resistance, up from 21 countries in

2008. Twenty-eight countries have completed surveys or are in the process of implementing them to classify the extent of transmitted HIV drug resistance. Quality assured results are available for 15 surveys. In 13 of these, transmitted HIV drug resistance was classified as low level and, in two (in Burkina Faso and Cameroon), it was classified as moderate level.

A survey conducted for the first time in Burkina Faso showed moderate levels of transmitted HIV drug resistance among a sample of HIV-positive women in their first pregnancy (Box 4.10). This calls for stepping up surveillance for and monitoring of HIV drug resistance to ensure that underlying programme bottlenecks can be addressed in a timely manner.

Box 4.10. Assessing transmitted HIV drug resistance in Ouagadougou, Burkina Faso

Between May 2008 and June 2009, Burkina Faso implemented the WHO methodology to classify transmitted HIV drug resistance in recently infected individuals (47). Specimens for HIV drug resistance testing were obtained from 52 consecutively diagnosed HIV-positive women attending antenatal care sites in Ouagadougou. All the women (aged 15-24 years) were pregnant for the first time, with no previous history of a diagnostic test for syphilis. In this population of young, HIV-positive pregnant women in Ouagadougou, the prevalence of transmitted HIV drug resistance was found to be between 5% and 15% for both NRTIs and NNRTIs, and thus classified as moderate according to the WHO methodology. Following WHO recommendations, Burkina Faso reviewed its treatment programme and launched an investigation into potential problems with continuous access to services, drug supply and drug quality. In addition, it also strengthened its adherence support programmes among populations receiving antiretroviral therapy. The survey should be repeated regularly to assess the level of transmitted HIV drug resistance in this population and in different geographical regions of the country.

4.1.6. Antiretroviral drug regimen

In 2010, the WHO AIDS Medicines and Diagnostics Service (AMDS) conducted the fourth annual survey on the distribution and composition of first- and second-line antiretroviral therapy regimens used in low- and middle-income countries.

A standardized questionnaire was sent to the ministries of health of 86 countries from all six WHO Regions (a list of countries is available at <http://www.who.int/hiv/amds/en/>) with the highest number of people receiving antiretroviral therapy as of December 2009. Seventy-six countries responded, reporting a total of 4 940 000 patients on antiretroviral therapy, representing 94.3% of the estimated 5 240 000 million people receiving antiretroviral therapy in resource-limited countries as of December 2009.

Table 4.8. Antiretroviral use, per drug and regimen, across low- and middle-income countries, 2009

Antiretroviral medicines ^a		59 low- and middle- income countries excluding countries from the Americas region)		17 countries in the Americas region	
		Proportion of first-line combinations containing the drug (%)	Proportion of second-line combinations containing the drug (%)	Proportion of first-line combinations containing the drug (%)	Proportion of second-line combinations containing the drug (%)
nRTI	3TC	94.2	31.6	91.1	75.0
	d4T	59.7	3.0	2.3	30.3
	AZT	32.1	47.2	71.3	27.8
	TDF	7.7	32.4	21.4	17.3
	ABC	0.4	22.3	4.0	14.0
	ddI	0.3	48.1	0.8	17.3
	FTC	5.4	15.5	7.9	2.6
NNRTI	NVP	60.7	1.1	12.4	5.1
	EFV	38.5	1.6	50.2	20.1
	ETV	0.0	0.0	0.0	0.0
Protease Inhibitors	LPV	0.4	92.7	20.9	37.9
	NFV	0.0	0.3	0.0	0.1
	IDV	0.1	0.9	0.0	5.9
	SQV	0.0	0.3	3.0	1.9
	ATV	0.0	0.0	12.3	17.7
	FPV	0.0	0.0	0.1	2.9

^a Regimens may contain more than one drug of the same class.

An initial analysis revealed that the 17 reporting countries from the Americas region (376 000 patients) presented a pattern of use of antiretrovirals that was notably different from the one observed in the remaining 59 low- and middle-income countries which participated in the survey (4 564 000 patients). In order to account for such differences, the results are presented separately by subgroup.

In the group of 59 low- and middle-income countries, 92.4% (4 218 000) of patients receiving antiretroviral therapy were adults. Of these, 97.5% were on first-line regimens, with 99.1% receiving treatment regimens in line with the 2006 WHO treatment guidelines. Of the patients, 59.7% were on a stavudine (d4T)-containing combination, 32.1% received a zidovudine (AZT)-based regimen and 7.7% used a tenofovir (TDF)-based combination (Table 4.8 and Figure 4.5).

In the same group of countries, only 2.4% (100 400 patients) of adults were on second-line regimens, with 87.2% of them receiving regimens in line with the 2006 WHO treatment guidelines. Ritonavir-boosted lopinavir (LPV/r) was the predominant protease inhibitor, used by 92.7% of patients receiving a second-line regimen. Importantly, though, 5.8% of adult patients on a second-line treatment followed a regimen that was not in accordance with WHO's normative guidance because they did not include a protease inhibitor (Figure 4.5). Only 1400 patients, or 0.01%, were reported to use salvage therapy.

In the 17 low- and middle-income countries of the Americas, patterns of antiretroviral use were noticeably

different (Figure 4.6). Adults also comprised the majority (364 000 or 96.9%) of people receiving antiretroviral therapy. Countries reported a majority of adults on first-line regimens (84.0%) with extensive use of a zidovudine-containing regimen (71.3%). Interestingly, though, an important proportion of adult patients on first-line treatment reported the use of a protease inhibitor (36.3%), and only a small number received either stavudine or nevirapine (2.3% and 12.4%, respectively).

Countries in the Americas also reported a higher rate of use of second-line (9.7%) and salvage regimens (6.3%) among adults, and the availability and use of a wider variety of protease inhibitors. Of the 6.3% (20 100) of adult patients on salvage therapy, most were on a quadritherapy. A few patients reported the use of more recent antiretroviral drugs, such as darunavir and raltegravir (used, respectively, by 0.7% and 0.6% of all patients).

Differences in the use of antiretroviral therapy were also observed between the two country groupings with respect to the treatment of children (Figures 4.7 and 4.8). In the group of 59 low- and middle-income countries, children represented 7.8% of people receiving antiretroviral therapy, and most (96.9%) were on first-line regimens (328 000 patients). Reported data showed that while 97.3% of first-line regimens followed the 2008 revision of the WHO treatment guidelines, this proportion, at 59.8%, was much lower for second-line combinations. It is worth noting that 14.6% of children received a second-line regimen without a protease inhibitor, contrary to the WHO treatment

Fig. 4.5. Composition and frequency of use of first- and second-line antiretroviral therapy regimens among adults in 59 low- and middle-income countries, excluding countries from the Americas Region, December 2009

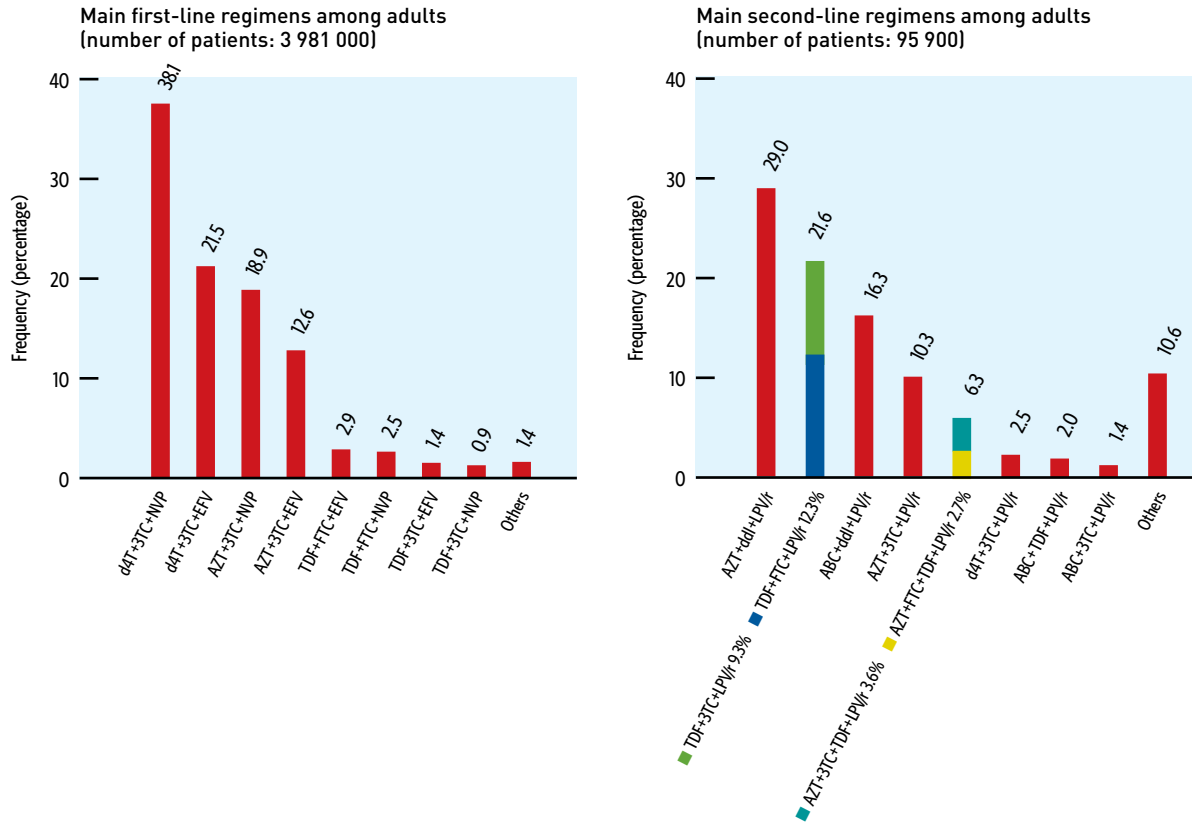


Fig. 4.6. Composition and frequency of use of first- and second-line antiretroviral regimens among adults in 17 low- and middle-income countries of the Americas Region, December 2009

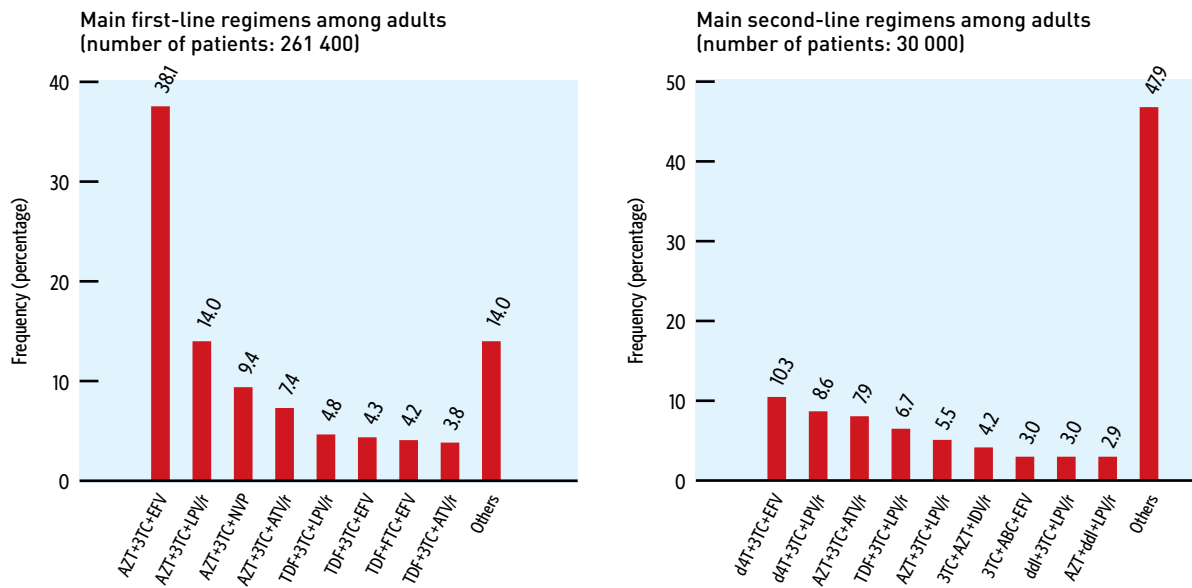


Fig. 4.7. Composition and frequency of use of first-line and second-line antiretroviral therapy regimens among children in 59 low- and middle-income countries, excluding countries from the Americas Region, December 2009

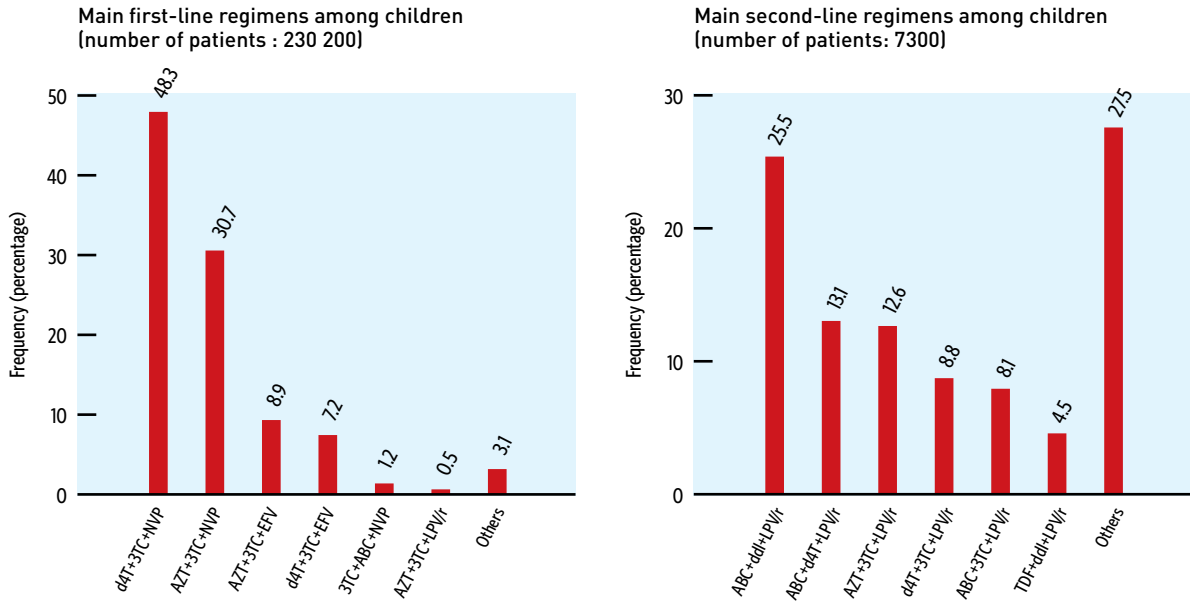
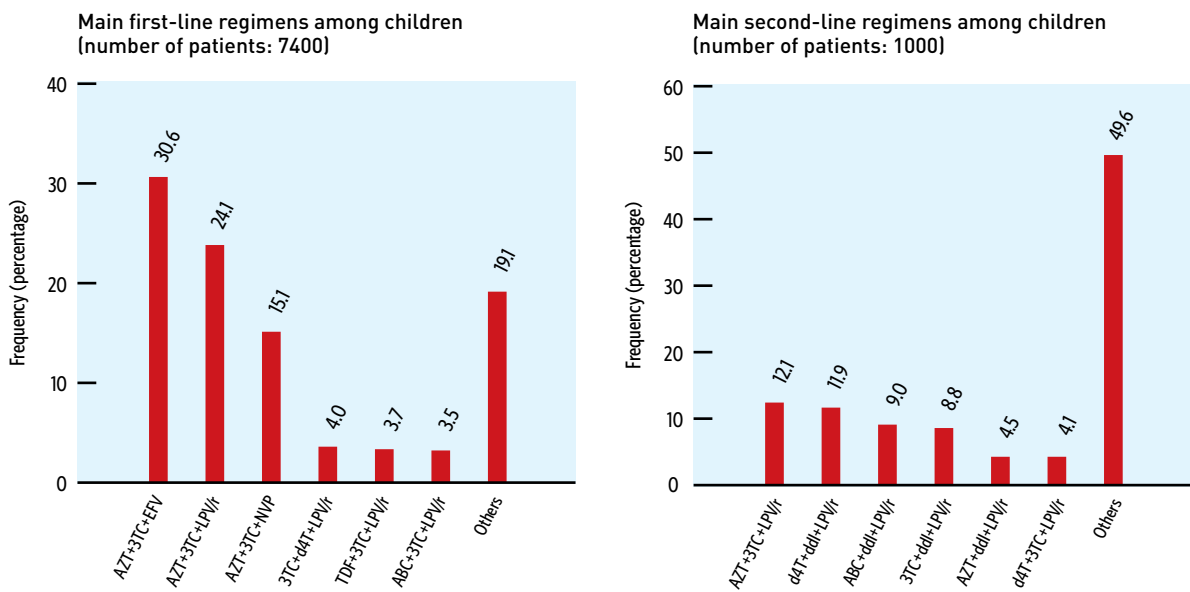


Fig. 4.8. Composition and frequency of use of first-line and second-line antiretroviral therapy regimens among children in 17 countries from the Americas Region, December 2009



guidelines. In the Americas Region, children represented 3.1% (11 700 patients) of the reported patient population on antiretroviral therapy, with a higher proportion of children on second-line regimens (11.7%).

A subset of 17 countries participated in all four consecutive surveys on use of antiretroviral drugs conducted between 2006 and 2009.¹ By December 2009, these 17 countries represented 49.1% (2 575 000) of the total 5 240 000 patients receiving antiretroviral therapy. In this subgroup, the use of stavudine in first-line combinations decreased from 67% in 2006 to 51.5% in 2009. On the other hand, the use of tenofovir increased and comprised 10.9% of first-line combinations, up from less than 1% in 2006 (Figure 4.9). Data on second-line regimens showed a reverse trend in tenofovir use, with a decrease in 2009 compared with 2008 (42.6% in 2009 and 56.5% in 2008).

The 2009 survey also demonstrates that an important number of low- and middle-income countries have already incorporated into their national treatment guidelines the new WHO recommendations on eligibility criteria and regimen choice for adults and adolescents (Box 4.1). In a subset of 54 countries that provided detailed information on national

treatment guidelines as of December 2009, 45² have already recommended initiation of antiretroviral therapy for patients with CD4 counts at or below 350 cells/mm³ and 33³ are actively shifting from stavudine-based to zidovudine- or tenofovir-containing regimens.

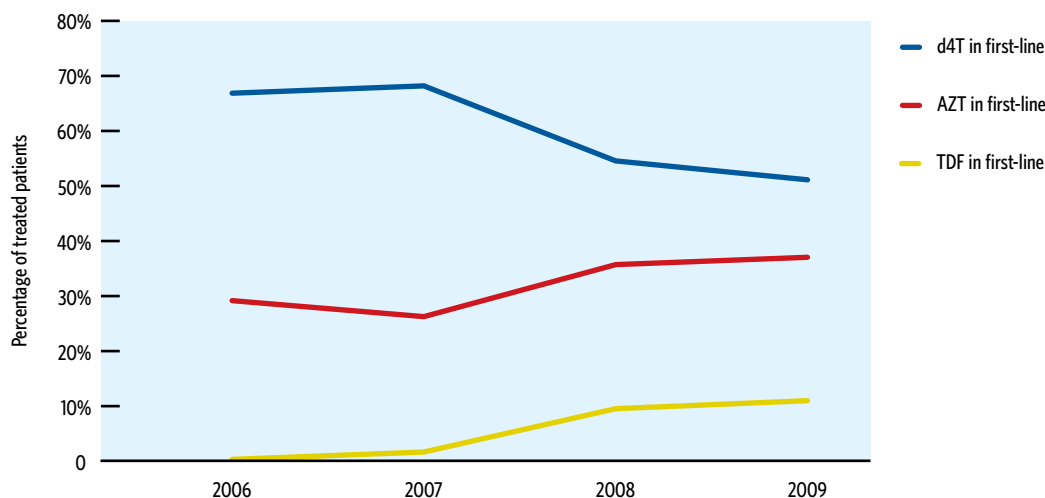
It remains critical to appropriately monitor actual antiretroviral use in order to adequately identify eventual discrepancies between guidelines and clinical practice, which can endanger patients' lives and undermine programme outcomes. This is particularly true as many countries face increased fiscal constraints and must cope with the double challenge of replacing stavudine with more expensive compounds while increasing the number of patients on treatment under the newly adopted set of eligibility criteria.

¹ The 17 countries are Burkina Faso, Burundi, Cambodia, Cameroon, Côte d'Ivoire, Ethiopia, India, Kenya, Lesotho, Namibia, Nigeria, Rwanda, Swaziland, the United Republic of Tanzania, Uganda, Zambia and Zimbabwe.

² Forty-five countries adopted this recommendation for all patients: Angola, Benin, Burkina Faso, Cameroon, Central African Republic, Cape Verde, Chad, China, Congo, Côte d'Ivoire, Eritrea, Gabon, Gambia, Ghana, Guinea, Indonesia, Iran, Kenya, Lesotho, Malawi, Mali, Morocco, Moldova, Namibia, Nigeria, Pakistan, Papua New Guinea, Saudi Arabia, Sierra Leone, Rwanda, Romania, Sao Tome, Seychelles, Senegal, Sudan, Swaziland, Tanzania, Togo, Ukraine, Viet Nam, Zambia and Zimbabwe. Three countries adopted the recommendation pertaining to pregnant women: Botswana, South Africa and the Democratic Republic of Congo.

³ Stavudine phase-out has already started in 33 countries: Angola, Botswana, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, China, Comoros, Côte d'Ivoire, Congo, Djibouti, Eritrea, Ethiopia, Ghana, Indonesia (tenofovir), Kenya, Lesotho, Liberia, Madagascar, Morocco, Moldova, Mozambique (zidovudine), Namibia, Rwanda, Senegal, Seychelles, South Africa, Sudan, Togo, Uganda, Ukraine. Five other countries either have or are developing a stavudine phase-out plan.

Fig. 4.9. Proportions of patients receiving stavudine (d4T), zidovudine (AZT) or tenofovir (TDF) in first-line regimens in 17 reporting countries, 2006–2009



Box 4.11. Pharmacovigilance

As HIV/AIDS treatment programmes are scaled up in low- and middle-income countries, adverse events linked with the use of antiretroviral medicines may compromise patients' well-being and safety. These include problems of toxicity, intolerance, drug-drug interactions, and adverse events linked with co-morbidities such as TB, hepatitis and malaria.

Pharmacovigilance is critically important to optimize patient adherence to treatment and treatment outcomes, and to ensure programme effectiveness. In the context of antiretroviral therapy, pharmacovigilance activities are also important for programmatic decision-making to regularly update national treatment, care and prevention guidelines, and to inform the initial selection, forecasting, procurement and distribution of antiretroviral drugs.

WHO recommends the development of national pharmacovigilance programmes for antiretroviral drugs. These programmes should focus on treatment monitoring and post-marketing surveillance based on passive and active methods, cohort event monitoring, pregnancy registries and special studies. In treatment sites, services providers should be trained and enabled to prevent, detect and assess adverse effects or other antiretroviral drug-related problems. Pharmacovigilance programmes should also contribute to create a "culture of safety" based on good communication of information about the benefits, harms and risks of drugs to practitioners, patients and the public.

A WHO Pharmacovigilance project for antiretroviral medicines funded by the Bill and Melinda Gates Foundation is based on the following major components: consensus on definitions, methods and tools, capacity building, research agenda and coordination and information-sharing.

In partnership with the Global Fund to fight AIDS, Tuberculosis and Malaria (Global Fund), WHO has developed a strategy based on best practices to stimulate the inclusion of pharmacovigilance in Global Fund proposals and pharmaceutical plans, as well as to identify and field-test effective pharmacovigilance processes and tools. These documents and tools are available online at <http://www.who.int/hiv/topics/pharmacovigilance/en/>

Bibliography

WHO. *A practical handbook for the pharmacovigilance of antiretroviral medicines*. Geneva, World Health Organization, 2009. (<http://www.who.int/hiv/pub/pharmacovigilance/handbook/en/index.html>, accessed 16 July 2010).

WHO. *Pharmacovigilance for antiretrovirals in resource-poor countries*. Geneva, World Health Organization, 2007. (www.who.int/entity/medicines/publications/PhV_for_antiretrovirals.pdf, accessed 16 July 2010).

WHO. *The safety of medicines in public health programmes: pharmacovigilance an essential tool*. Geneva, World Health Organization, 2006. (www.who.int/medicines/areas/quality_safety/safety_efficiency/Pharmacovigilance_B.pdf, accessed 16 July 2010).

The Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring. *Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre*. The Uppsala Monitoring Centre, 2000. (www.who.int/medicinedocs/en/d/Jh2934e/, accessed 16 July 2010)

WHO. *Clinical management of adverse events linked to antiretroviral medicines*. Geneva, WHO, 2010 (in press).

4.1.7. Antiretroviral drug price

The Global Price Reporting Mechanism (GPRM) for antiretroviral drugs, established in 2004, provides information on the transaction prices of antiretroviral drugs purchased in 123 countries, including 43 low-income, 48 lower-middle-income and 32 upper-middle-income countries.

Reported data show that prices of the six most used first-line regimens recommended by WHO in low- and middle-income countries have decreased between 1% and 36% between 2008 and 2009, contributing to wider treatment availability (Figure 4.10).¹ Regionally, prices tend to be lower in sub-Saharan African than in other regions. Average prices paid for second-line regimens remain relatively high in all regions (with some exceptions in certain low-income countries), where few or no prequalified generic alternatives are available.

4.1.7a. Prices of first-line regimens in low-income countries²

The median price paid for first-line treatments in low-income countries in 2009 ranged from US\$ 81 per person per year for the fixed-dose combination of d4T+3TC + NVP (the most widely used combination) to US\$ 613 for the most expensive fixed-dose combination of TDF+FTC+EFV (Figure 4.10). The weighted median³ price of the six most widely used first-line regimens (representing 96% of prescribed first-line treatments in low-income countries) was US\$ 137 per person per year in 2009, 3% lower than the average median price in 2008. Although modest, this drop occurred in spite of the wider adoption of more expensive tenofovir-based regimens. The decline in drug prices between 2006 and 2009 (54%) can be attributed to the sustained scaling up of treatment programmes, the growing transaction volumes

¹ Additional figures with data on lower-middle- and upper-middle-income countries are available online at <http://www.who.int/hiv/data/en/>.

² Countries with a gross national income per capita of US\$ 975 or less

³ The weighted median price is the sum of individual regimen median price weighted/multiplied by the percentage of patients in the general population using that specific regimen.

Fig. 4.10. Median annual cost (in US dollars) of first-line antiretroviral drug regimens for adults in low-income countries (LIC), 2006–2009

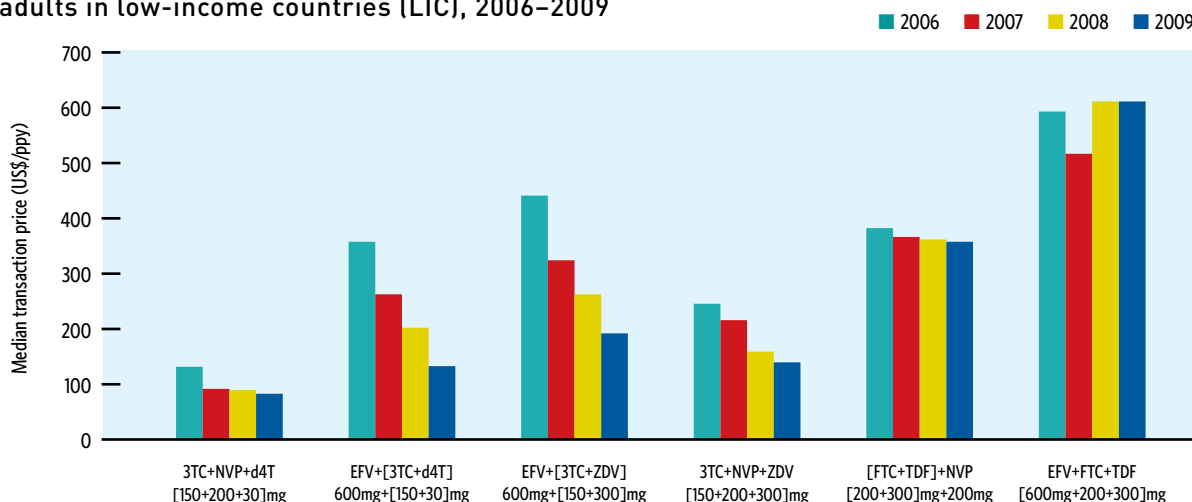
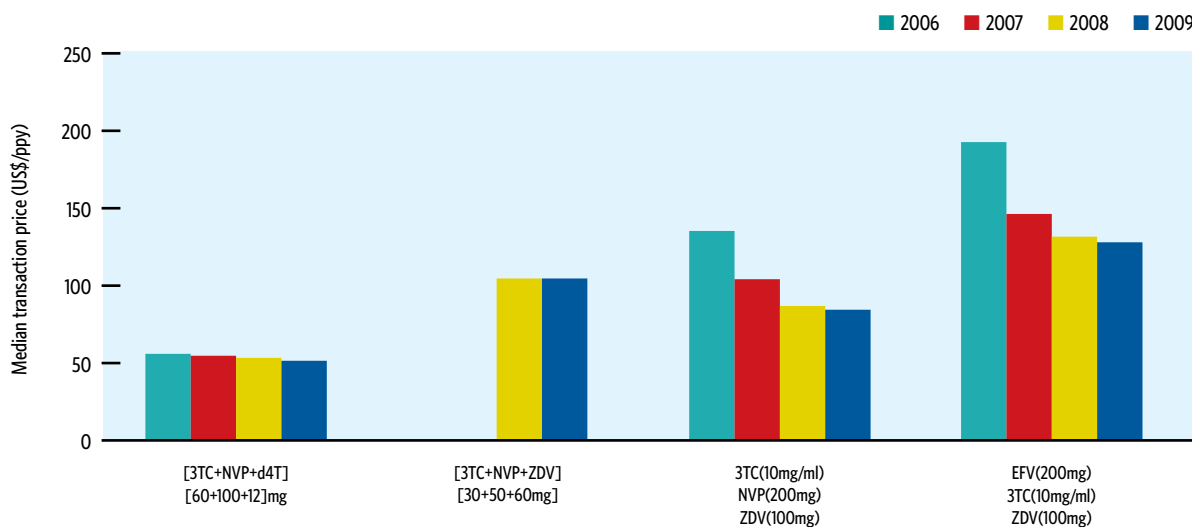


Fig. 4.11. Median annual cost (in US dollars) of first-line antiretroviral drug regimens for children (weighing 10 kg or more) in low-income countries (LIC), 2006–2009



and predictability of demand, the competition between a growing number of products prequalified by WHO and the favourable pricing policies by pharmaceutical companies.

In 2009, the combination of d4T+3TC+NVP replaced AZT+3TC+NVP as the most commonly prescribed formulation for children (weighing 10 kg or more). Its average price declined from US\$ 57 per person per year in 2006 to US\$ 52 in 2009. Average prices of other combinations continued to fall as well (Figure 4.11). Such price decreases can be attributed to economies of scale associated with a larger market for paediatric formulations, successful negotiations with major generic manufacturers and development of fixed-dose combination formulations for children.

4.1.7b. Prices of first-line regimens in lower-middle-income countries¹

Median prices in 2009 ranged from US\$ 76 per person per year for the least expensive regimen of d4T+3TC+NVP, to US\$ 667 per person per year for the most expensive regimen of TDF+FTC+EFV. In the same year, the weighted median price of the six most widely used combinations in first-line regimens was US\$ 141 per person per year, a decrease of 13% from the previous year's price.

The most commonly used combination among children (weighing 10 kg or more) was d4T+3TC+NVP and its price fell from US\$ 70 per person per year in 2006 to US\$ 55 in 2009.

¹ Countries with a gross national income per capita of between US\$976 and US\$ 3855

4.1.7c. Prices of first-line regimens in upper-middle-income countries¹

In 2009, in upper-middle-income countries, median prices ranged from US\$ 88 per person per year for the least expensive regimen of d4T+3TC + NVP to US\$ 635 per person per year for TDF+FTC+NVP.² In the same year, the weighted average median price of the six most widely used combinations in first-line regimens was US\$ 202 per person per year. This represents a 21% increase from the median price observed in 2008, a fact partially explained by the inclusion of more expensive TDF-containing regimens in first-line therapy.

In 2009, only AZT-based regimens were reported for children's formulations (weighing 10 kg or more). The price of the most frequently used combination, AZT+3TC+NVP, reached US\$ 177, a decline of 16% since 2006.

4.1.7d. Prices of second-line regimens in low- and middle-income countries

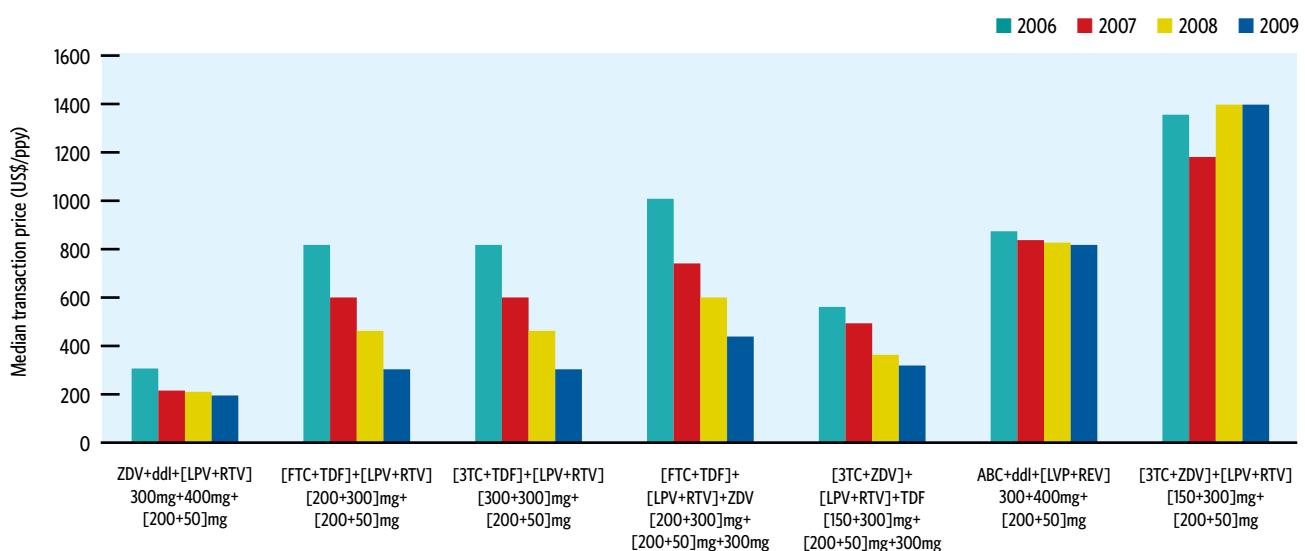
Prices paid for second-line regimens also declined in 2009, but remained more expensive than first-line regimens

across low-income (Figure 4.12), lower-middle-income and upper-middle-income countries. In 2009, the median cost of the most commonly used second-line regimen of ZDV+ddl+LPV/r was US\$ 853 per person per year in low-income countries, US\$ 1378 in lower-middle-income countries and US\$ 3638 in upper-middle-income countries. The median cost of [FTC +TDF] + LPV/r, the second most commonly used second-line regimen, was US\$ 819 per person per year in low-income countries, US\$ 1392 in lower-middle-income countries and US\$ 3551 in upper-middle-income countries. Actual prices paid for second-line regimens vary greatly between countries. The decline in the prices of second-line drugs between 2006 and 2009 can be attributed to the prequalification of generic alternatives for abacavir (ABC), LPV/r and TDF, the patent expiry of ddl, scaling up of treatment programmes and new pricing policies by pharmaceutical companies, which increased competition between WHO-prequalified products. However, as the number of people who need access to second-line regimens continues to grow, addressing the high cost of second-line regimens will become increasingly important to ensure the most cost-effective use of available resources.

1 Countries with a gross national income per capita of between US\$ 3856 and US\$ 11 905

2 Most expensive combination for which sufficient transaction data are available

Fig. 4.12. Median annual cost (in US dollars) of second-line antiretroviral drug regimens for adults in low-income countries (LIC), 2006–2009



Box 4.12. Scaling up the response to viral hepatitis

Greater attention must be devoted to addressing coinfection of HIV with viral hepatitis, especially hepatitis B and hepatitis C. With the expansion of antiretroviral therapy since 2003, many coinfecting patients have been able to access antiretroviral therapy to treat HIV. However, treatment for viral hepatitis has not been scaled up concomitantly, leaving many people living with HIV and viral hepatitis exposed to the complications of hepatitis B and C infections, including fatal liver disease.

The revised WHO antiretroviral therapy guidelines for adults and adolescents recommend that antiretroviral therapy be initiated, irrespective of WHO disease stage or CD4 cell count, in all patients with HIV/hepatitis B coinfection and chronic active hepatitis B¹ when treatment is indicated for hepatitis B. The revised guidelines recommend tenofovir (TDF)- and lamivudine (3TC)- (or emtricitabine)-containing antiretroviral regimens in all HIV/hepatitis B coinfecting individuals needing treatment. In case of failure of antiretroviral therapy, TDF and 3TC (or emtricitabine) should be continued for activity against hepatitis B virus and the second-line regimen should include other drugs with anti-HIV activity. Hepatitis C can be effectively treated with a combination therapy of pegylated interferon and ribavirin. Treatment for hepatitis C infection can lead to clearance of the virus, thus avoiding longer-term liver damage. Treatment, however, requires enhanced laboratory capacity for diagnosis and monitoring of treatment effectiveness.

Resolution WHA63.18, adopted at the 63rd World Health Assembly in May 2010, recognized viral hepatitis as a public health issue and called for the implementation of comprehensive responses. It also called upon all Member States to improve epidemiological surveillance systems and to strengthen laboratory capacity, where necessary, in order to generate reliable information for guiding prevention and control measures (49).

¹ The current diagnosis of chronic active hepatitis in well-resourced settings is based on histological parameters obtained by liver biopsy and/or the availability of hepatitis B virus DNA testing, neither of which is usually available in resource-limited settings. A global definition of chronic active hepatitis in the context of resource-limited settings based on clinical signs and simpler laboratory parameters is under discussion.

4.2. Collaborative TB/HIV activities

HIV-related TB remains a serious challenge for the health sector's response to HIV. Recent data show that, of the 9.4 million incident TB cases worldwide in 2008, an estimated 1.4 million were among people living with HIV. Around 520 000 deaths from TB occurred among people living with HIV, equivalent to 26% of the estimated 2 million deaths from HIV and 29% of the 1.8 million deaths from TB in that year (50). The risk for TB is 20–37 times higher in people living with HIV than in the general population, depending on the prevalence of HIV in the population (51).

Sub-Saharan Africa continues to account for the majority of people living with HIV and TB in the world. In 2008, around 78% of estimated HIV-positive TB cases were in this region, of which around one quarter was living in South Africa. The South-East Asia Region, mainly India, accounts for 13% of the remaining cases.

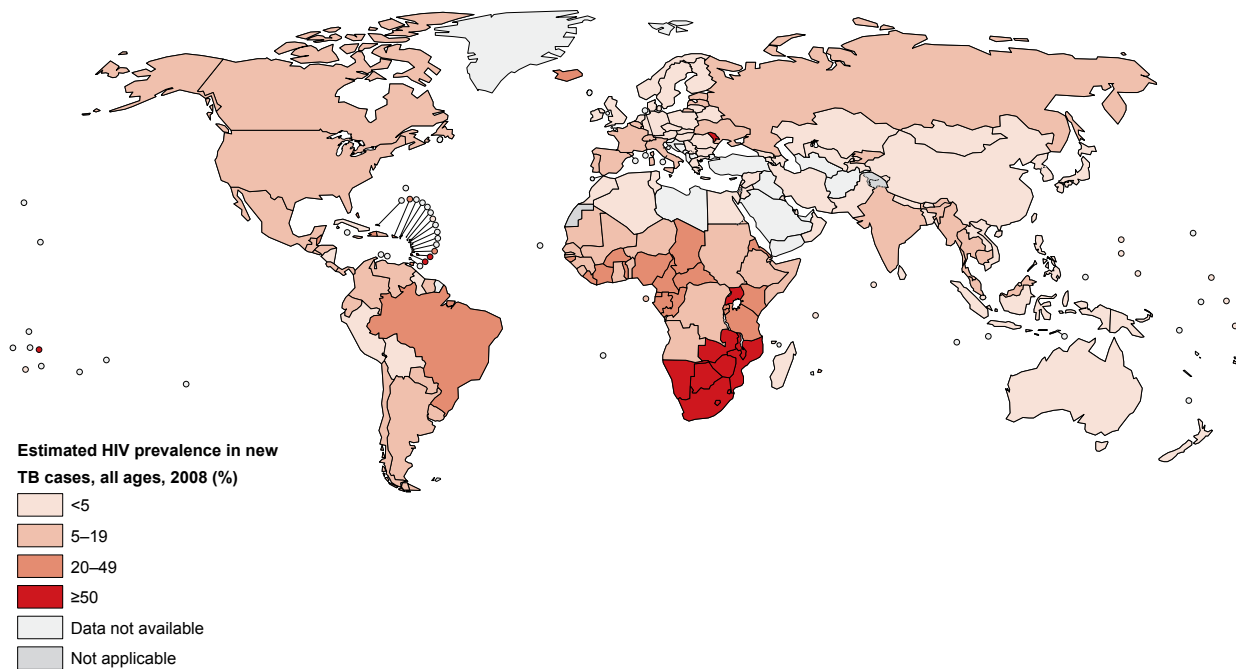
Data on drug-resistant forms of TB show that of, the 9.4 million incident TB cases in 2008, an estimated 440 000 were cases of multidrug-resistant TB. The region of Eastern Europe and Central Asia is especially severely affected. In addition, 58 countries and territories reported at least one case of extensively drug-resistant TB in 2008. People living with HIV may be at higher risk for drug-resistant forms of TB due to difficulties and delays in diagnosis, lack of access to antiretroviral therapy and complications of concomitant treatment with TB and antiretroviral therapy, poor implementation of isoniazid preventive therapy, and

inadequate TB infection control measures, with increased mortality and greatly reduced survival time (52–56).

Collaborative activities between national TB and HIV programmes are essential to prevent, diagnose and treat TB among people with HIV and HIV among those with TB. These include establishing *mechanisms for collaboration* (such as coordinating bodies, joint planning, surveillance, and monitoring and evaluation); *decreasing the burden of HIV among people with TB* (with HIV testing and counselling, co-trimoxazole preventive therapy, antiretroviral therapy, and HIV prevention, care and support); and *decreasing the burden of TB among people with HIV* (with the *three I's for HIV/TB* intensified case-finding, TB prevention with isoniazid preventive therapy and/or antiretroviral therapy, and infection control for TB).

Different models for the delivery of integrated HIV and TB services have been implemented in several countries with promising results. In India, for example, TB and HIV services are provided separately with strengthened cross-referral. Provision of HIV testing in TB clinics and TB screening for inpatients in medical wards and HIV-positive outpatients has been used in Rwanda, while integrated models with “one-stop service” for TB patients with HIV have been reported in South Africa. Each model, however, has advantages and disadvantages and is highly dependent on contextual issues and policy choices. Nevertheless, irrespective of the model chosen, earlier access to HIV testing and counselling, antiretroviral therapy and TB preventive or curative treatment is key to prevent excess morbidity and mortality from TB.

Fig. 4.13. Estimated HIV prevalence among new TB cases, 2008



Box 4.13. Towards effective integrated services for HIV and TB in Ethiopia

In Ethiopia, the implementation of collaborative TB/HIV activities started in nine sites in 2004. The establishment of the TB/HIV Technical Working Group in 2007 accelerated the expansion of implementation to reach 848 sites in 2009 (57). HIV/AIDS and TB care and treatment are provided in separate clinics located in close proximity. TB clinics offer HIV-related services, mainly the provision of provider-initiated HIV testing and counselling, post-test counselling and referral to the HIV care unit which, in turn, offers co-trimoxazole prophylaxis, other drugs for opportunistic infections and antiretroviral therapy. The number of TB patients with known HIV status has increased rapidly from 20 723 in 2007, to 56 040 in 2009, or more than doubled over a three-year period (58). Co-trimoxazole preventive therapy and antiretroviral therapy were provided to 11 098 and 7516 HIV-positive TB patients, respectively, in 2009 compared to 4529 and 2658, respectively, in 2007. It is estimated that currently 95% of TB patients are tested for HIV and that almost all health staff working with TB or HIV/AIDS have been trained in TB/HIV collaborative activities.

In spite of continued progress, several programmatic challenges still need to be addressed to further scale up the implementation of integrated TB and HIV activities. Greater emphasis must be placed on improving the coordination among TB/HIV entities at the regional level, training TB health-care workers on antiretroviral therapy and chronic care, ensuring the continuous availability of TB/HIV guidelines, making available instruction manuals and information materials at all clinics, initiating antiretroviral therapy and HIV care services at TB clinics, and implementing a robust monitoring and evaluation framework for TB and HIV collaborative activities. Engagement with communities in designing, delivering and evaluating HIV/TB-related activities must be further strengthened to ensure maximum programme effectiveness.

4.2.1. Decreasing the burden of HIV among people with TB and their community¹

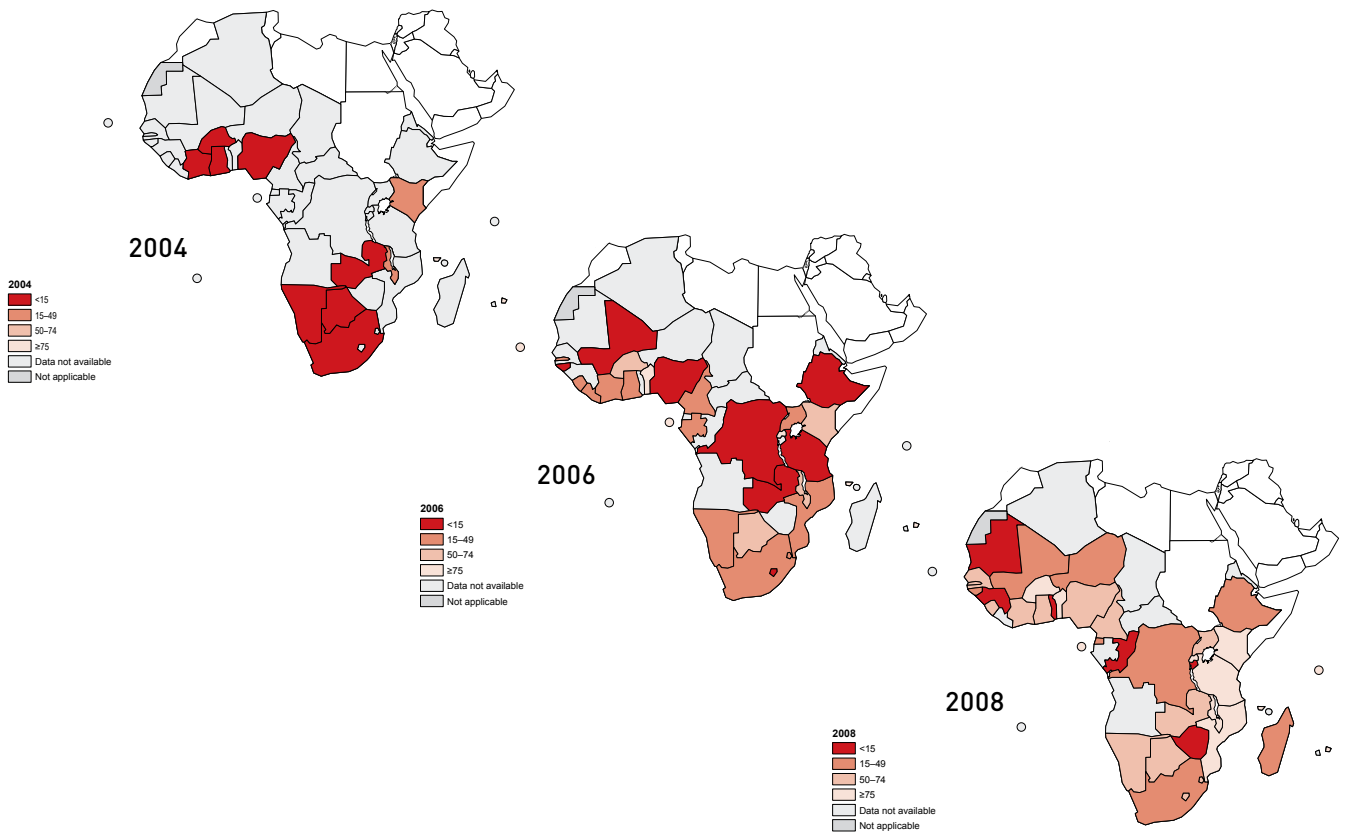
HIV counselling and testing is recommended for everyone presenting with signs and symptoms of TB and people with confirmed TB. There has been progress in expanding HIV testing and counselling for TB patients over the past years. Almost 1.4 million TB patients knew their HIV status in 2008 (22% of notified cases compared to 16% in 2007 and 3.2% in 2004). In 2008, the rate of HIV testing among TB patients was 45% in Africa, more than a tenfold increase since 2004 (Figure 4.14), and reached 79% in the WHO European Region.

Co-trimoxazole has been proven to reduce morbidity and mortality among people living with HIV and TB. In 2008, among coinfecting patients knowing their HIV-positive status, around 230 000 patients (71%) were receiving it. Based on data reported by countries, coverage estimates have remained stable over the past few years (77% in 2006, 67% in 2007).

Antiretroviral therapy is a priority life-saving intervention for people living with HIV. Among people living with HIV diagnosed with TB, WHO recommends that antiretroviral therapy be started as soon as possible after starting TB treatment, regardless of the immunological stage (Box 4.1). The number of people living with HIV and TB who received antiretroviral therapy across all reporting countries increased from about 67 000 in 69 reporting countries

¹ This section draws largely from *Global Tuberculosis Control: a short update to the 2009 report*, WHO, 2010. Additional references used are cited where relevant.

Fig. 4.14. Rates of HIV testing among TB patients WHO African Region, 2004–2008



Box 4.14. Impact of antiretroviral therapy on TB incidence and TB treatment outcomes

Scientific evidence increasingly supports the fact that antiretroviral therapy can reduce the incidence of, and morbidity and mortality from, TB. Antiretroviral therapy has been shown to reduce TB incidence by up to 90% at the individual level (59) and by 60% at the population level (60).

Impact of antiretroviral therapy on the incidence of TB

A clinical trial conducted in Haiti, comparing early (CD4 counts at or below 350 cells/mm³) versus standard (CD4 counts at or below 200 cells/mm³) initiation of antiretroviral therapy showed that early initiation, in addition to an important positive impact on survival, decreased the incidence of TB by approximately 50% (61). In Brazil, between 1995 and 2001, rates of recurrent TB, either due to reinfection or reactivation, were halved after the introduction of antiretroviral therapy (62). The use of highly active antiretroviral therapy has also been associated with more rapid conversion of smears and cultures (63).

A mathematical model has investigated the short- and long-term impacts of antiretroviral therapy on the incidence of TB. Once universal access is achieved, the incidence of HIV-related TB should fall by 50%, provided people start antiretroviral therapy within five years of seroconversion.¹

Impact of antiretroviral therapy on the outcomes of TB treatment

Scientific evidence also indicates that antiretroviral therapy can appreciably reduce TB-related morbidity and mortality in people living with HIV. Observational studies conducted both in resource-limited and high-income settings have shown that antiretroviral therapy is associated with significant reductions in mortality risk from TB of between 54% and 95% on an adjusted basis (64).

Observational studies have shown an important correlation between early initiation of antiretroviral therapy during TB treatment and lower mortality rates (65–71). These studies have concluded that the risk of death was reduced when antiretroviral therapy was started as early as possible during the course of TB treatment compared to delayed initiation of antiretroviral therapy. In response to such developments, WHO now recommends antiretroviral therapy for everyone living with HIV and diagnosed with TB, irrespective of immunological status, and as soon as possible after starting TB treatment.

¹ Williams B, personal communication, 2010

in 2006, to 125 000 people in 77 reporting countries in 2008 and 173 000 in 101 countries in 2009. Of these, 141 000 people were in sub-Saharan Africa, 14 000 in East, South and South-East Asia, 8500 in Latin America and the Caribbean, 8100 in Eastern Europe and Central Asia, and 1000 in North Africa and the Middle East. They represented 17% of the estimated TB/HIV cases in these reporting countries, a figure considerably lower than the estimated coverage of antiretroviral therapy for all HIV patients in low- and middle-income countries. Given the increasing evidence of access to testing for TB patients, and better linkages between TB and HIV services, this gap may reflect the weaknesses of reporting access to care among TB/HIV patients. However, this might also reflect poorer access to antiretroviral therapy for TB patients. Indeed, data from eight countries that accounted for 18% of the estimated global burden of HIV-positive TB cases in 2007 showed that there are more than five decentralized TB treatment centres for every facility providing antiretroviral therapy (51).

4.2.2. Decreasing the burden of TB among people with HIV

Decreasing the burden of TB among people with HIV relies on the *Three I's for HIV/TB* strategy: isoniazid preventive treatment, prevention of TB with intensified case finding, and infection control for TB (Box 4.15). The poor implementation of the *Three I's for HIV/TB* strategy remains a major concern for the control of these dual epidemics. In 2009, 43% of reporting countries (48 out of 112) indicated that isoniazid preventive treatment was a part of their package of interventions for people living with HIV; 60% reported having implemented intensified case finding for TB prevention and 51% had a TB infection control policy.

It remains critical for managers of HIV and TB programmes to work closely together and with affected communities to scale up and ensure that people living with HIV have access

to the *Three I's for HIV/TB* as part of universal access to high-quality comprehensive prevention, care and treatment of HIV infection and TB (64).

4.3. Looking ahead

As of December 2009, 1.2 million additional people were on antiretroviral therapy, the largest year-on-year increase on record. Yet, revised treatment guidelines for antiretroviral therapy in adults and adolescents, which now recommend therapy to be initiated at an earlier stage of disease, increased the number of eligible patients in low- and middle-income countries by 45%, from 10.1 million to 14.6 million. This means that, in spite of continued progress, with less than 3 months to December 2010, only 36% of patients in need of antiretroviral therapy in low- and middle-income countries currently have access to it.

While achieving universal access may now require higher upfront investments, these are likely to be more than compensated in the medium term by savings as morbidity and mortality rates fall and costs associated with hospitalizations and palliative care drop. Such positive dynamics underscore the need to accelerate efforts to scale up access to treatment and care interventions.

In addition to accelerated efforts, new models are necessary to enhance the efficiency and effectiveness of service delivery, including antiretroviral treatment provision, and expand coverage and increase the impact of HIV interventions in general.

More must be done to strategically integrate HIV/AIDS interventions into national health services, strategies and plans, including those for sexual, reproductive, maternal and child health, tuberculosis, sexual transmitted infections

Box 4.15. The *Three I's for HIV/TB* guidelines

The revised draft of the "WHO guidelines for intensified case finding and isoniazid preventive therapy for tuberculosis for people living with HIV in resource-constrained settings" recommends the use of a simplified screening algorithm that includes four clinical symptoms – current cough, fever, weight loss, night sweats – to identify those eligible for either isoniazid preventive treatment or further diagnostic work-up for TB and other conditions. While chest radiography is no longer mandatory before starting isoniazid preventive treatment, the guidelines do support its use when feasible to increase the sensitivity of the screening. Building on the 1998 UNAIDS/WHO isoniazid preventive treatment policy, the new guidelines strongly recommend at least six months of isoniazid preventive treatment for children and adults, including pregnant women, people receiving antiretroviral therapy and for those who have successfully completed TB treatment. In addition, a 36-month course of isoniazid preventive treatment is now conditionally recommended in high HIV- and TB-prevalent settings. The revised guidelines emphasize that a tuberculin skin test is not a requirement for initiating isoniazid preventive treatment for people living with HIV. However, where feasible, tuberculin skin testing can assist in identifying those who would benefit most from isoniazid preventive treatment. The revised guidelines also emphasize isoniazid preventive treatment as a core component of HIV prevention and care services, and recommend that TB prevention be considered as a central responsibility of AIDS programmes and HIV service providers. The re-conceptualized guidelines no longer discuss isoniazid preventive treatment as an isolated intervention for people living with HIV, but recommend it as part of a broader TB prevention package along with infection control for TB, intensified TB case finding and the provision of antiretroviral therapy.

and harm reduction. At the same time, special approaches remain necessary to address the particular circumstances and needs of those groups usually not reached through standard service delivery channels, including populations at greater risk of HIV infection.

Multiple programmatic bottlenecks along the continuum of care, from treatment initiation to long-term therapy maintenance, still hinder effective responses in many low- and middle-income countries and threaten their sustainability. The Treatment 2.0 Initiative, launched by WHO and UNAIDS, seeks to address them through a holistic perspective aimed at raising the quality of services delivered and dramatically reducing the cost of interventions.

Timely initiation of antiretroviral therapy – often an issue because people do not know their HIV status and because of underlying stigma and discrimination – is necessary to avoid the high mortality rates observed in the first year after adults and children initiate treatment. Expanding access to HIV testing and counselling services, including through provider-initiated approaches, must continue to be a priority to ensure timely diagnosis of HIV infection.

Greater attention must also be paid to the quality of services and interventions, as only high-quality treatment programmes can sustain appropriate levels of retention and adherence to antiretroviral therapy. Indeed, low adherence and retention are two critical reasons for poor treatment outcomes among people receiving antiretroviral therapy. In addition to directly affecting personal well-being, poor adherence and retention rates may accelerate the shift from first- to more expensive, and often unavailable, second-line regimens at an unnecessarily early stage.

Despite reductions in drug prices over the past ten years, overall costs of antiretroviral therapy programmes have continued to rise, as more patients initiate antiretroviral therapy and more need to move from first- to second-line combinations, whose prices are still higher than entry-level

regimens. Therefore, additional efforts are necessary to reduce their prices and increase their availability in low- and middle-income countries. Nevertheless, although increasing drug affordability is important, potential gains are now highest in the area of reducing non-drug-related costs of providing treatment, such as inpatient care and staff-related expenses.

While current regimens can successfully lower morbidity and mortality among people receiving treatment, their long-term toxicities can still negatively affect critical treatment outcomes. In addition, treatment monitoring often requires highly specialized equipment and laboratory technicians. Dramatic acceleration of access to treatment thus requires the development of simpler, less toxic and less resistance-prone treatment regimens, as well as cheaper and simplified diagnostic and monitoring tools. Ensuring that all people in need have access to treatment will also maximize the preventive effect of antiretroviral therapy. Indeed, it is estimated that this could result in an annual reduction in new HIV infections of up to one third. Moreover, optimizing HIV treatment coverage can yield other important health prevention benefits, including much lower rates of tuberculosis among people living with HIV.

These novel approaches will only be successfully designed and implemented with substantially strengthened community mobilization and involvement in programme management and service delivery. In addition, greater community participation is key to improving treatment access and adherence. Indeed, community-based approaches that build trust, protect human rights and provide opportunities for socialization directly improve the ability of people to use HIV services and access antiretroviral therapy. This is particularly essential for those groups who are most marginalized and discriminated against, including migrants, injecting drug users, sex workers and men who have sex with men. [🌐](#)

Box 4.16. Reducing stigma and discrimination in health-care facilities in Ghana (72)

HIV-related stigma has been identified as one of the principal obstacles to HIV prevention and scaling up testing and treatment worldwide. Fear of stigma, also known as “anticipated stigma”, falls more heavily in vulnerable populations, such as women, key affected groups and the poor, who are often at greater risk for HIV acquisition (73,74). Unfortunately, populations most in need of access to HIV services are often those with the highest levels of fear about the stigma they might experience in health facilities (73).

Recent research has identified three main drivers of HIV stigma, which are consistent across contexts (75): (i) lack of awareness and knowledge of HIV-related stigma and discrimination, (ii) fear of acquiring HIV through everyday contact with infected people, and (iii) linking people living with HIV with behaviours considered improper or immoral.

Studies show that interventions aimed at decreasing stigma in health facilities can change health workers’ attitudes and behaviours towards people living with HIV. The underlying drivers of HIV-related stigma may be addressed by creating awareness of what stigma is and the benefits of reducing it, fostering motivation for change, addressing fears and misconceptions about HIV transmission, discussing “taboo” topics such as gender, violence, sexuality and injecting drug use, and providing skills to challenge stigma and change behaviour (76,77).

In mid-2006, Quality Health Partners (QHP), in partnership with the Strengthening HIV/AIDS Response Partnerships (SHARP) project, the Ghana Sustainable Change Project and the National AIDS Control Programme (NACP), launched the high-impact package of HIV and AIDS interventions (HIP) initiative to complement the national scale-up of comprehensive HIV services. At the same time, it aimed to address the issue of stigma and improve facility-community linkages.

In relation to stigma, HIP includes: 1) training in stigma reduction and infection prevention for clinical and non-clinical health workers (tailored to each group); 2) training in infection prevention for family or friends who are caregivers of clients; and 3) action plans for client-oriented, provider-efficient services to address facility-specific stigma-related issues (e.g. to improve privacy, confidentiality and client-provider interaction).

In 2008–09, a rapid appraisal of six of 25 QHP-supported hospitals implementing HIP and their clients was undertaken to measure the prevalence of stigma and discriminatory attitudes and practices among staff, and the effectiveness of the HIP training in mitigating them. Although the study was not a complete impact evaluation, a number of notable results emerged.

- The majority of clients and health workers reported declines in the major drivers of stigma, especially a reduction in the fear of casual transmission and of moralizing attitudes, though clients’ fears of indirect disclosure remained.
- Clients reported that though HIV-related stigma had declined in other units of the hospital, it still negatively impacted upon the quality of care.
- “Anticipated” HIV stigma by health workers did not appear to be an obstacle for the majority of most-at-risk populations using testing, treatment and care services.
- The HIP interventions reportedly increased health workers’ willingness to care for HIV-positive people.
- Both health workers and clients reported a decline in discriminatory practices towards people living with HIV.

A number of recommendations resulted from the appraisal. First, it is necessary to maintain and strengthen, with the necessary budget allocations, the training content and activities aimed at reducing stigma and discrimination, while incorporating more follow-up activities and refresher trainings to enhance retention of the material and its implementation. The appraisal also suggested the need to prioritize issues that groups at higher risk for HIV infection (including men who have sex with men, sex workers and injecting drug users) identify as primary obstacles to the uptake of health prevention and care services, such as lack of adequate protection of client confidentiality. The appraisal also drew attention to the importance of strengthening linkages between stigma reduction activities targeting health facilities and those targeting communities, as health workers’ behaviour in the workplace may be negatively influenced by discriminatory attitudes and perceptions carried over from the communities they live in.

References

1. *Rapid advice: antiretroviral therapy for HIV infection in adults and adolescents*. Geneva, World Health Organization, 2009. (<http://www.who.int/hiv/pub/arv/advice/en/index.html>, accessed 15 July 2010).
2. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the use of antiretroviral agents in HIV-1-Infected adults and adolescents*. Department of Health and Human Services. December 1, 2009:1-161. (<http://www.aidsinfo.nih.gov/ContentFiles/AdultsandAdolescentGL.pdf>, accessed on 25 January 2009).
3. Anonymous. Southern African Clinicians Society Guidelines: antiretroviral therapy in adults. *Southern African Journal of HIV Medicine*, 2008, 29:18-31.
4. Recomendações para Terapia Anti-retroviral em Adultos Infectados pelo HIV: 2008/ Ministério da Saúde, Secretaria de Vigilância em Saúde. Programa Nacional de DST e Aids. 7a Ed. - Brasília: Ministério da Saúde, 2008.
5. Kitahata M et al. Effect of early versus deferred antiretroviral therapy for HIV survival. *New England Journal of Medicine*, 2009, 360:1815-1826.
6. Sterne JA et al.; When to Start Consortium. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. *Lancet*, 2009, 373:1352-1363.
7. Sax P, Baden L. When to start antiretroviral therapy - ready when you are? *New England Journal of Medicine*, 2009, 360:1897-1899.
8. *The Global Fund 2010: innovation and impact*. Geneva, Global Fund to Fight AIDS, Tuberculosis and Malaria, 2010.
9. Latest results [web site]. *Technical note on PEPFAR's reporting methodology*. Washington, DC, United States President's Emergency Plan for AIDS Relief, 2010 (<http://www.pepfar.gov/2009results/>, accessed 8 August 2010).
10. Press room [website]. Making a difference: funding. Washington, DC, United States President's Emergency Plan for AIDS Relief, 2010 (<http://www.pepfar.gov/press/index.htm> accessed 8 August 2010).
11. UNAIDS. Publications: Reference Group reports [web site]. Geneva, UNAIDS Reference Group on Estimates, Modelling and Projections, 2009 (<http://www.epidem.org/publications.htm> accessed 9 July 2010).
12. Granich R et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*, 2009, 373: 48-57.
13. Stover J et al. The Spectrum projection package: improvements in estimating mortality, ART needs, PMTCT impact and uncertainty bounds. *Sexually Transmitted Infections*, 2008, 84 Suppl 1: i24-i30. And (for 2009 version): www.unaids.org/en/KnowledgeCentre/HIVData/Epidemiology/EPI_software2009.asp
14. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. *Tropical Medicine & International Health*, 2010, 15(s1):1-15.
15. Tassie JM et al. Trends in retention on antiretroviral therapy in national programs in low-income and middle-income countries. *Journal of Acquired Immune Deficiency Syndromes*, 2010, 54:437-41.
16. Harries AD et al. Strategies to improve patient retention on antiretroviral therapy in sub-Saharan Africa. *Tropical Medicine & International Health* 2010, 15(s1):70-75.
17. Fairall LR et al. Effectiveness of antiretroviral treatment in a South African program: a cohort study. *Archives of Internal Medicine*, 2008, 168:86-93.
18. Bassett IV et al. Who starts antiretroviral therapy in Durban, South Africa?... not everyone who should. *AIDS*, 2010, 24 (Suppl 1):S37-S44.
19. McGuire M et al. Vital status of pre-ART and ART patients defaulting from care in rural Malawi. *Tropical Medicine & International Health*, 2010, 15(s1):55-62.
20. Amuron B et al. Mortality and loss-to-follow-up during the pre-treatment period in an antiretroviral therapy programme under normal health service conditions in Uganda. *BMC Public Health*, 2009, 9:290.
21. Rajaratnam JK et al. Worldwide mortality in men and women aged 15-59 years from 1970 to 2010: a systematic analysis. *Lancet*, 2010, 375:1704-1720.

22. Egger M, Boule A. Population effect of scaling up ART in resource-poor settings. *Lancet*, 2008, 371:1558-1559.
23. Beck EJ et al. for the National Prospective Monitoring System Steering Group. Decreased morbidity and use of hospital services in English HIV-infected individuals with increased uptake of anti-retroviral therapy 1996-1997. *AIDS*, 1999, 13:2157-2164.
24. Makombe SD et al. Assessing the quality of data aggregated by antiretroviral treatment clinics in Malawi. *Bulletin of the World Health Organization*, 2008,86:310-314.
25. The Global Fund to Fight AIDS, Tuberculosis and Malaria. *5-Year evaluation: study area 3*. (<http://www.theglobalfund.org/en/terg/evaluations/5year/> accessed 22 June 2010).
26. Walton DA et al. Integrated HIV prevention and care strengthens primary health care: lessons from rural Haiti. *Journal of Public Health Policy*, 2005, 25:137-158.
27. Sanne I et al. Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial. *Lancet*, 2010, 376:33-40.
28. Herbst AJ et al. Adult mortality and antiretroviral treatment roll-out in rural KwaZulu-Natal, South Africa. *Bulletin of the World Health Organization*, 2009, 87:754-762.
29. Quinn TC et al. Viral load and heterosexual transmission of HIV 1. Rakai Study Group. *New England Journal of Medicine*, 2000, 342:921-929.
30. Attia S et al. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS*, 2009, 23:1397-1404.
31. Donnell D et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet*, 2010, 375:2092-2098.
32. Wood E et al. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users prospective cohort study. *British Medical Journal*, 2009, 338:b1649.
33. Das-Douglas M et al. Decreases in community viral load are associated with a reduction in new HIV diagnoses in San Francisco. In: *17th Conference on Retroviruses and Opportunistic Infections (CROI), San Francisco, USA, 16-19 February 2010* (abstract 33; <http://www.retroconference.org/2010/Abstracts/38232.htm>, accessed 3 August 2010).
34. Castel A et al. Monitoring the impact of expanded HIV testing in the District of Columbia using population-based HIV/AIDS surveillance data. In: *17th Conference on Retroviruses and Opportunistic Infections (CROI), San Francisco, USA, 16-19 February 2010*,(abstract 34; <http://www.retroconference.org/2010/Abstracts/38192.htm> accessed 3 August 2010).
35. Walensky RP et al. Scaling up antiretroviral therapy in South Africa: the impact of speed on survival. *Journal of Infectious Diseases*, 2008, 197:1324-1332.
36. Velasco-Hernandez JX, Gershengorn HB, Blower SM. Could widespread use of combination antiretroviral therapy eradicate HIV epidemics? *Lancet Infectious Diseases*, 2002, 2:487-493.
37. Montaner JS et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet*, 2006, 368:531-536.
38. Walensky RP et al. Test and treat DC: modeling the impact of a comprehensive HIV strategy in the US Capitol. *5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 19-22 July 2009, Cape Town, South Africa* (abstract no. LBPECO4; <http://www.ias2009.org/pag/Abstracts.aspx?AID=3748>, accessed 16 July 2010).
39. Charlebois E et al. Effect of expanded ART strategies on the MSM HIV epidemic in San Francisco. In: *17th Conference on Retroviruses and Opportunistic Infections (CROI), San Francisco, USA, 16-19 February 2010* (abstract 996; <http://www.retroconference.org/2010/Abstracts/39042.htm>, accessed 13 March 2010).
40. De Luca A, Prosperi M, Bracciale L. Resistance considerations in sequencing of antiretroviral therapy in low-middle income countries with currently available options. *Current Opinion in HIV and AIDS*, 2010, 5:27-37.
41. Hamers RL et al. The status of HIV-1 resistance to antiretroviral drugs in sub-Saharan Africa. *Antiviral Therapy*, 2008, 13:625-639. [Review]. Erratum in: *Antiviral Therapy*, 2008, 13:1129.
42. *Report on the 2008 national HIV sentinel survey*. Windhoek, The Republic of Namibia Ministry of Health and Social Services, 2008 (<http://www.healthnet.org.na/documents/reports/2008%20National%20HIV%20Sentinel%20Survey%20Report.pdf>, accessed on 15 August 2010).

43. World Health Organization [website]. *Country health profile: Namibia*. Geneva, World Health Organization, 2010 (<http://www.who.int/countries/nam/en/> accessed August 2010).
44. Bennett DE et al. The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. *Antiviral Therapy*, 2008,13 (Suppl 2):1-13.
45. World Health Organization. *HIV drug resistance: early warning indicators*. April 2010 update. (http://www.who.int/hiv/topics/drugresistance/hiv_dr_early_warning_indicators.pdf, accessed on 18 August 2010).
46. Jordan MR et al. World Health Organization surveys to monitor HIV drug resistance prevention and associated factors in sentinel antiretroviral treatment sites. *Antiviral Therapy*, 2008, 13 (Suppl. 2):15-23.
47. Bennett DE et al. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. *Antiviral Therapy*, 2008 13 (Suppl. 2):25-36.
48. Myatt M, Bennett DE. A novel sequential sampling technique for the surveillance of transmitted HIV drug resistance by cross-sectional survey for use in low resource settings. *Antiviral Therapy*, 2008, 13 (Suppl. 2):37-48.
49. Resolution WHA63.18. Viral hepatitis. In: *Sixty-third World Health Assembly, Geneva, 21 May 2010*. Geneva, World Health Organization, 2010 (WHA63/A63_R18), (http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R18-en.pdf, accessed 14 July 2010).
50. WHO. *Global Tuberculosis Control: a short update to the 2009 report*. Geneva, Switzerland, World Health Organization, 2010.
51. Getahun H et al. HIV Infection-associated tuberculosis: the epidemiology and the response. *Clinical Infectious Disease*, 2010, 50 (Suppl. 3):S201-S207.
52. Wells CD et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. *Journal of Infectious Diseases*, 2007, 196 (Suppl. 1):S86-S107.
53. Dubrovina I et al. Drug-resistant tuberculosis and HIV in Ukraine: a threatening convergence of two epidemics? *International Journal of Tuberculosis and Lung Disease*, 2008, 12:756-762.
54. *Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response*. Geneva, Switzerland, World Health Organization, 2010.
55. Havlir DV et al. Opportunities and challenges for HIV care in overlapping HIV and TB epidemics. *Journal of the American Medical Association*, 2008, 300:423-430.
56. Kawai V et al. Tuberculosis mortality, drug resistance, and infectiousness in patients with and without HIV infection in Peru. *The American Society of Tropical Medicine and Hygiene*, 2006, 75:1027-1033.
57. Meaza Demissie. "Situation analysis for the provision of HIV prevention, care and treatment services, including antiretroviral therapy for HIV positive TB patients using TB service points in Ethiopia," Report, November 26, 2009 (mimeo).
58. *WHO global TB control report*. Geneva, WHO, 2011 (in press).
59. Miranda A et al. Impact of antiretroviral therapy on the incidence of tuberculosis: the Brazilian experience, 1995-2001. *PLoS One*, 2007, 2:e826.
60. Middelkoop K et al. Can antiretroviral therapy contain a previously escalating TB epidemic in a HIV prevalence community? *5th IAS conference on HIV Pathogenesis, Prevention and Treatment; 2009 Cape Town, South Africa, 2009*.
61. Severe P et al. Early versus standard antiretroviral therapy for HIV-infected adults in Haiti. *New England Journal of Medicine*, 2010, 363:257-265.
62. Golub JE et al. Recurrent tuberculosis in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS*. 2008, 22:2527-2533.
63. Nahid P et al. Treatment outcomes of patients with HIV and tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, 2007, 175:1199-1206.
64. Granich R et al. Prevention of tuberculosis in persons infected with HIV. *Clinical Infectious Diseases*, 2010, 50 (Suppl. 3):67-S70.
65. Lawn SD, Kranzer K, Wood R. Antiretroviral therapy for control of the HIV-associated tuberculosis epidemic in resource-limited settings. *Clinics in Chest Medicine*, 2009, 30:685-699.

66. Blanc FX et al. Treatment strategies for HIV-infected patients with tuberculosis: ongoing and planned clinical trials. *Journal of Infectious Diseases*, 2007, 196 (Suppl. 1):S46-S51.
67. Abdool Karim SS et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *New England Journal of Medicine*, 2010, 362:697-706.
68. Velasco M et al. Effect of simultaneous use of highly active antiretroviral therapy on survival of HIV patients with tuberculosis. *Journal of Acquired Immune Deficiency Syndromes*, 2009, 50:148-152.
69. Varma JK et al. HIV care and treatment factors associated with improved survival during TB treatment in Thailand: an observational study. *BMC Infectious Diseases*, 2009, 9:42.
70. Tabarsi P et al. Early initiation of antiretroviral therapy results in decreased morbidity and mortality among patients with TB and HIV. *Journal of the International AIDS Society*, 2009, 12:14.
71. Blanc FX et al. Significant enhancement in survival with early (2 weeks) vs. late (8 weeks) initiation of highly active antiretroviral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis. *XVIII International AIDS Conference 2010, Vienna, Austria, 18-23 July 2010* (abstract THLB106).
72. Quality Health Partners, Engender Health. A rapid appraisal of HIV-related stigma and discrimination reduction interventions in selected health facilities in Ghana (final draft). January 2009 (http://www.ghanahqhp.org/fileadmin/user_upload/QHP/HIV_Stigma_Rapid_Appraisal_Report_09.pdf, accessed 29 August 2010).
73. Wolfe WR et al. The impact of universal access to antiretroviral therapy on HIV stigma in Botswana. *American Journal of Public Health*, 2008, 98:1865-1871.
74. Parker R, Aggleton P. HIV and AIDS-related stigma and discrimination: a conceptual framework and implications for action. *Social Science and Medicine*, 2003, 57:15-24.
75. UNAIDS. *Reducing HIV stigma and discrimination: a critical part of national AIDS programmes, a resource for national stakeholders in the HIV response*. Geneva, UNAIDS, 2008.
76. Nyblade L et al. *Disentangling HIV and AIDS stigma in Ethiopia, Tanzania and Zambia*. Washington, DC, International Center for Research on Women, 2003.
77. Ogden J, Nyblade L. *Common at its core: HIV-related stigma across contexts*. Washington, DC, International Center for Research on Women, 2005.