

REVIEW

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KEY WORDS: *human immunodeficiency virus; acquired immunodeficiency syndrome; highly active antiretroviral therapy; antiretroviral treatment scale – up; developing countries; trade – related aspects of intellectual property rights*

ABBREVIATIONS

AIDS = acquired immune deficiency syndrome
CAPRISA = Center for the AIDS Program of Research in South Africa
CD 4 = cluster of differentiation 4 (glycoprotein expressed on surface of T-helper cells)
HIV = human immune deficiency virus
HAART = highly active anti-retroviral therapy
MTCT = mother-to-child transmission
NNRTIs = non-nucleoside reverse transcriptase inhibitors
NRTIs = nucleoside reverse transcriptase inhibitors
NGO = non-governmental organization
PEP = post-exposure prophylaxis
PEPFAR = US President's Emergency Plan for AIDS Relief
PIs = protease inhibitors
PMTCT = preventing mother-to-child transmission
TB = tuberculosis
TRIPS = trade-related aspects of intellectual property rights
UNAIDS = Joint United Nations Program on HIV/AIDS
WHO = World Health Organization
WTO = World Trade Organization

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Access to Affordable Highly Active Anti – Retroviral Therapy (HAART) for HIV / AIDS Patients. Where Do We Stand?

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ABSTRACT

BACKGROUND: The human immunodeficiency virus (HIV) epidemic remains a major global public health challenge, with a total of 33.4 million people living with HIV worldwide. In 2008 alone, 2.7 million people were newly infected with HIV. Unfortunately, the majority of patients with HIV infection worldwide live in resource poor areas where access to therapy is severely limited.

OBJECTIVE: This review summarizes the progress noted during the recent years concerning antiretroviral therapy scale up in resource-limited settings and analyzes the economic, social and legal framework of services already provided.

RESULTS: The 2010 WHO report states that among 144 low- and middle-income countries reporting program data, eight had already achieved universal access to antiretroviral therapy at the end of 2009, providing treatment to at least 80% of patients in need. Furthermore, 15 countries had achieved the 80% target for coverage with antiretroviral prophylaxis to prevent mother-to-child transmission of HIV. An increase of over 1.2 million people, including women and children receiving antiretroviral therapy was noted by the end of 2009. Health care facilities have expanded and as a result, the average number of people receiving antiretroviral therapy per health care facility has increased. Moreover, task shifting has been applied, with promising results.

CONCLUSIONS: Although there is considerable room for improvement, HIV programs have had a positive impact on equal, affordable and early antiretroviral therapy provision to those who need it most. Special approaches though, remain necessary to address the particular circumstances and needs of those populations at greater risk for HIV infection. Rights-based national strategies must include special efforts to reach the poorest and those who are socially excluded. Interventions must be designed and realized in ways that ensure equity in access for all.

INTRODUCTION

Since its identification in 1981 as a novel entity, acquired immune deficiency syn-

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drome (AIDS) has infected more than 60 million and killed 20 million people worldwide.¹ The introduction of antiretroviral therapy in 1995-96 has led to its gradual evolution from a fatal disease to a chronic condition.² Antiretroviral therapy has been shown to prolong survival in persons with human immune – deficiency virus (HIV) infection. Significant results have been demonstrated with the introduction of double³ as well as triple combination therapy.⁴ The remarkable increase in the use of these double and triple combination regimens has led to major declines in AIDS mortality.⁵ Nevertheless, the majority of patients with HIV infection worldwide live in resource poor areas where access to therapy is severely limited. In 2008, an estimated 33.2 million people were living with HIV, with 68% of all adults living with HIV, 90% of the world's infected children and 76% of all AIDS deaths being encountered in the Sub-Saharan Africa.⁶ Although HIV represents a global health priority, its management and care is very complex and challenges the health care systems worldwide. Many of the countries with the highest rates of HIV infection have insufficient access to antiretroviral therapy. In addition to the actual cost of anti-HIV drugs, other major obstacles include the deficient health-care structures, the lack of laboratory facilities and health-care technology, the lack of medical training, as well as administrative delays. Moreover, stigma and discrimination continue to be experienced by people affected, leading to decreased treatment adherence. Coverage of prevention interventions is still insufficient and the current economic recession has prompted even wealthy countries to reassess their commitment to HIV programs.⁷

WHERE DO WE STAND?

ANTIRETROVIRAL THERAPY GUIDELINES – WHEN TO START

According to the World Health Organization (WHO) antiretroviral therapy guidelines, all patients with HIV infection and a cluster of differentiation 4 (CD4) cell count at or below 350 cells/mm³ should be started on antiretroviral therapy. Adolescents, adults, as well as pregnant women, are all included, regardless of whether they have clinical symptoms or not.⁷ Guidelines from wealthy countries however, recommend even earlier initiation of anti-retroviral agents, at a CD4 cell count of 500 cells/mm³ or above.⁸ More specifically, updated recommendations for the management of HIV- infected adults in the developed world, as reported by the Department of Health and Human Services Panel on antiretroviral guidelines for adults and adolescents, include guidelines whose strength varies according to the number of CD4 cell count before treatment:

- CD4 count <350 cells/mm³ (**AI**)
- CD4 count 350 to 500 cells/mm³ (**AII**)
- CD4 count >500 cells/mm³ (**BIII**)

Recommendations are rated with a letter (A, B, or C) that represents the strength of the recommendation and with the figures I, II, or III that signify the quality of the evidence (A: strong recommendation, B: moderate, C: optional; I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints, II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes, III: Expert opinion)

Regardless of CD4 count, initiation of therapy is strongly recommended for individuals with • pregnancy (**AI**), • history of an AIDS-defining illness (**AI**), • HIV-associated nephropathy (**AII**), • HIV/hepatitis B virus coinfection (**AII**), as well as for • patients who are at risk of transmitting HIV to sexual partners (heterosexuals (**AI**) or • other transmission risk groups (**BIII**).

With regards to the consistency of the specific regimens, more than 20 antiretroviral drugs in 6 classes are available in the developed world. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), C-C chemokine receptor type 5 (CCR5) antagonists, and integrase strand transfer inhibitors (INSTIs) (Table 1).⁹⁻¹¹

The WHO guidelines for patients in developing countries state that first-line therapy should include a non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTI), one of which should be zidovudine (AZT) or tenofovir (TDF). The second-line therapy should consist of a ritonavir (RTV)-boosted protease inhibitor plus two NRTIs, one of which should be AZT or TDF, depending on what was used in the first-line regimen. The preferred protease inhibitors are ritonavir-boosted atazanavir (ATZ) or lopinavir/ritonavir (LPV/r).⁷

Overall, antiretrovirals are still underused relative to need in resource – limited settings, and they still reach people with too much delay. After the new recommendations of the WHO, a significant step has been made towards improving the efficacy of treatment in developing countries as well as preventing transmission of the virus. It is estimated that the number of people who are now in urgent need of treatment has increased to 14 million, raising thus the necessity for stronger actions and a more essential engagement towards the affected communities.¹²

Although the use of highly active anti-retroviral therapy (HAART) has been proven to be very effective in prolonging survival of HIV infected patients, some of the drugs, especially the ones mostly used in poor countries, cause significant side – effects. Hepatotoxicity,¹³ osteomalacia and Fanconi syndrome, for example, are noted after use of tenofovir.⁹ Stavudine and navirapine have also been accused of causing long – term toxicities.¹⁴ The former has been correlated with pancreatitis, steatosis,⁹ peripheral neuropathy and lipoatrophy. The 2010 WHO guidelines¹⁵ clearly recommend phasing out of the drug,

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY – CURRENT STATUS

TABLE 1. Antiretroviral Drugs

DRUG CLASS	Generic Name / Abbreviation	Formulation	Fixed-Dose Combination
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	Abacavir / ABC	Ziagen	Trizivir (ABC with ZDV+3TC) Epzicom (ABC with 3TC)
	Didanosine / ddI	Videx / Videx EC	
	Emtricitabine / FTC	Emtriva	Atripla (FTC with EFV+TDF) Complera (FTC with RPV+TDF) Truvada (FTC with TDF)
	Lamivudine / 3TC	Epivir	Combivir (3TC with ZDV) Epzicom (3TC with ABC) Trizivir (3TC with ZDV+ABC)
	Stavudine / d4T	Zerit	
	Tenofovir Disoproxil Fumarate / TDF	Viread	Atripla (TDF with EFV+FTC) Complera (TDF with RPV+FTC) Truvada (TDF with FTC)
	Zidovudine / ZDV	Retrovir	Combivir (ZDV with 3TC) Trizivir (ZDV with 3TC+ABC)
	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	Efavirenz / EFV	Sustiva
Etravirine / ETR		Intelence	
Nevirapine / NVP		Viramune or Viramine XR	
Rilpivirine / RPV		Edurant	Complera (RPV with TDF +FTC)
Protease Inhibitors (PIs)	Atazanavir / ATV	Reyataz	
	Darunavir / DRV	Prezista	
	Fosamprenavir / FPV / (a prodrug of amprenavir [APV])	Lexiva	
	Indinavir / IDV	Crixivan	
	Lopinavir + Ritonavir / LPV/r	Kaletra	
	Nelfinavir / NFV	Viracept	
	Ritonavir / RTV	Norvir	
	Saquinavir / SQV	Invirase	
Tipranavir / TPV	Aptivus		
Integrase Inhibitor	Raltegravir / RAL	Isentress	
Fusion Inhibitor	Enfuvirtide / T20	Fuzeon	
CCR5 Antagonist	Maraviroc / MVC	Selzentry	

CCR5 = C-C chemokine receptor type 5.

unfortunately though, due to low cost, stavudine containing regimens are still being used¹⁶ increasing the risk of lipodystrophy in patients who receive it.¹⁷

PRICE AND LEGAL FRAME

The management of HIV infection is representative of

what health care inequalities denote. Antiretroviral therapy became broadly available in developed countries in 1996, but it was only in 2002 when treatment programs were established in developing countries with the exception of Brazil, Thailand, Senegal and Botswana. The latter were providing antiretroviral therapy for adults through the public-sector health care

facilities as early as 2000. Regrettably, antiretroviral therapy services for children were initiated much later and continue to be limited.^{18,19}

The price of antiretroviral therapy was initially prohibitive for patients living in poor countries since they were available only from originator companies. These companies controlled the patents on medicines which cost 10,000 – 15000 \$ /person/year.²⁰

Global political mobilization as well as vigorous action from non – governmental organizations (NGOs) and people living with HIV led to the accomplishment of a dramatic drop of prices of first-line antiretroviral therapy. As a result, today more than five million patients in the developing world have access to antiretroviral therapy.²¹ More specifically, according to the Global Price Reporting Mechanism, there was a decline of first-line drug prices for both adults as well as the pediatric population between 2006 and 2009 in low-income countries. The cost of second-line regimens also declined, still remaining though more expensive than first-line regimens.²²

This achievement was a result of a series of events that started almost a decade ago. In 2000 an Indian pharmaceutical company named Cipla produced generic antiretrovirals at very low cost, forcing thus the big pharmaceutical companies to reduce their prices. It was in May 2000 when five pharmaceutical companies announced the Accelerating Access Initiative, offering price discounts on antiretroviral treatment in developing countries. However, the prices still remained too high compared with the prices offered by generic manufacturers.²³ The production of generic drugs not only brought the prices down, but also simplified HIV/AIDS treatment. In 2001, Cipla produced a combination of three antiretrovirals into a single pill. Although the company was not the only one that produced fixed – dose combination pills, it was the first to produce the fixed – dose combination of stavudine, lamivudine and nevirapine, a course of therapy recommended by WHO at the time.²⁴ Fixed – dose combination pills are in many ways advantageous both for patients and for health – care providers. Their most important benefits, the increased adherence and the consequent reduced incidence of drug resistance, have made it the basis of treatment programs in developing countries.²⁵

This was of course possible because India did not have to comply with Trade – Related Aspects of International Property Rights (TRIPS) legislation at the time. Since 2005 developing countries that are members of the World Trade Organization (WTO), such as India, Thailand and Brazil, have to obey and abide by TRIPS rules and issue patents. This has complicated the antiretroviral treatment's delivery because although patents have expired on a number of first-line AIDS drugs, patents still exist on most new and second-line medicines. Consequently, the new drugs are only available in countries that are able to cover the high cost. Poor countries are forced to wait until their patent expires or the proprietary prices are decreased.²⁶

In light of these concerns, the WTO proposed two procedures by which generic drugs under patents may be produced; the voluntary licensing and the compulsory licensing agreement. The former refers to a license a government, an individual, or an organization can request from a patent holder to allow generic drugs to be supplied during a public health emergency, either through imports or by local production. The drawback of voluntary licenses is that they depend on the goodwill of the patent holder, and can be long – lasting to negotiate. The compulsory license is a government license that enables someone other than the patent owner to copy patented products legally. Disadvantages include the predefined limited drug quantities that can be produced and the fact that the domestic market is the one that should be mainly supplied, making it difficult for poor countries that lack technological support to access generic drugs that are produced abroad.²⁷

In 2003, WHO and the Joint United Nations Program on HIV/AIDS declared the lack of antiretroviral treatment to be a global public health emergency and announced the “3 by 5” campaign. This campaign aimed at achieving to get three million people on antiretrovirals by 2005. The campaign was supported by newly available funding from governments such as the Global Fund and the United States President's Emergency Plan for AIDS Relief (PEPFAR) and led to access of generic medicines in considerable amounts.²⁸ It is reported that by 2008, 95% of the global donor-funded antiretroviral market consisted of generics, mainly from India.²⁹ The amount of generic antiretrovirals purchased by PEPFAR grew from 15% to 89% from 2005 to 2008.³⁰

Another way to handle intellectual property was the Medicines Patent Pool which was established by UNITAID, an organization that facilitates the purchase of drugs for HIV, malaria and tuberculosis (TB), hosted by WHO. It represents a conventional way of making voluntary licenses available, offering legal assurance to all parties involved. Patent holders have to make licenses available so that generic companies will be allowed to produce low-cost generics for use in developing countries. Companies that receive licenses from the pool will pay a fee of their sales to the patent owners.³¹ In September 2010, the US National Institutes of Health became the first patent holder to license its patents to the Medicines Patent Pool. Although the pool confronts challenges, it is a promising initiative aiming at making markets work better and facilitate overall distribution of HAART to those who face problems accessing therapy.³²

The free trade agreement, another legal outline (mainly between India and Europe) inflicting intellectual property protection on drugs, became an entity of division. Some criticize the free trade agreements' provisions, as disastrous for public health,³³ whilst others argue that intellectual property protection does not constitute a significant obstacle to access to medicines.³⁴ The former assert that members of the European Free Trade Agreement have strong interests such as data

exclusivity and extended patent terms. This, in turn, delays the introduction of generic drugs and goes beyond TRIPS agreement, weakening thus the distribution of medicines to people who need them. The latter claim that although India looses TRIPS flexibility, the Free Trade Agreement is not, after all, a major barrier to accessing therapy.

Patients in need of antiretrovirals in the developing world currently have a non drug resistant form of the virus, and can therefore receive first-line therapy. As treatment though becomes more widespread, people stay on treatment for longer and resistance increases, the high price of second-line drugs is going to become a major issue.⁷

AVAILABILITY AND HEALTH CARE FACILITIES

Health care facilities that provide antiretroviral treatment are important components of the antiretroviral scale-up programs. It is reported by WHO that there has been an increase of 36% in their number during the years 2008-2009, as provided by data from 99 countries. The average number of people receiving antiretroviral treatment per health care facility has also increased during the same time period. Interestingly, health care facilities in the Sub-Saharan Africa continue to treat more people per site than in the rest of the world.⁷

Scaling up treatment in endemic settings requires antiretroviral treatment provision by existing primary health care facilities wherever possible. Moving beyond the primary health care clinic and into the community is necessary,^{35,36} since this way the drugs are brought closer to those who need them and who cannot even afford their transportation to primary health care spots.³⁷ Decentralization was proven to be very effective as it has increased adherence wherever applied. Moreover, studies have compared outcomes in hospitals and health care centers and have found no difference in the quality of care provided.^{35,38,39}

The lack of specialized scientists who could offer their expertise to HIV infected patients in limited resource settings has led to the idea of ‘Task-shifting’, a program recommended by WHO as a way to overcome the lack of health care workers and the subsequent inadequate care provision. Nurses and clinical workers commence patients’ treatment and counselors provide HIV testing and adherence. The program has been implemented in some countries and studies report that it is found to be equivalent to programs run by physicians.^{36,40,41}

Decentralized treatment and task shifting must be supported by new simplified tests. Such tests must be easily performed even by minimally trained health care workers. Viral load and CD4 measurement for example is currently performed by complex and expensive tests. By 2012, smaller, fully automated devices and by 2013, ‘dipstick’- type CD4 tests and even simpler viral load tests will be available. This way, adherence problems, as well as treatment failure will be detected on time and consequently, resistance shall be avoided. Moreover, a new molecular TB test is expected by 2011 which

will be able to detect TB much more easily among people who are infected both with TB and HIV.⁴²

Another major issue of concern in low and middle- income countries is the management of drug stock-outs. All the sectors involved must be in close collaboration so as to distribute and relocate potential abundance of drugs as needed. As reported by WHO, 36 of the 94 countries reported at least one or more stock-out of antiretroviral drugs in health care facilities in 2009, compared to 31 out of 90 countries in 2008 and 25 out of 66 countries in 2007.⁷

PROGRESS OF ACCESS TO ANTIRETROVIRAL THERAPY

An increase of over 1.2 million people receiving antiretroviral treatment was noted at the end of 2009, worldwide. The greatest increase was observed in Sub-Saharan Africa, while the smallest was monitored in Latin America, possibly due to the already achieved high levels of coverage of most large countries of the region. Zimbabwe is being reported to have raised the number of patients receiving antiretroviral treatment by 50% between December 2008 and 2009.⁷

The global fund to fight AIDS, tuberculosis and malaria and the US President’s emergency plan for AIDS relief (PEPFAR) remained the two major international sources of funding for antiretroviral treatment programs in low- and middle- income countries in 2009. Based on WHO 2010 guidelines, eight low- and middle- income countries had already achieved universal access to antiretroviral treatment, that is providing it to at least 80% of people in need.

With regards to children, there has been an increase of 29% in antiretroviral treatment uptake during 2009. Overall antiretroviral therapy coverage however, was lower among children than among adults in low and middle- income countries. This is due to the fact that sub-Saharan Africa accounts for 89% of children needs, but has an estimated coverage rate of 26%. Antiretroviral coverage was higher for women, estimated at 39% compared with 31% among men.⁷

According to WHO 2011 news release, there has been globally an increase in access to HIV services which has led to 15% reduction of new infections (Figure 1).⁴³

A total of 56% coverage for antiretroviral therapy and 64% uptake of preventing mother-to-child transmission (PMTCT) services have been reported in Eastern and Southern Africa. In Asia, 4.8 million people receive antiretroviral treatment, half of them living in India. Interestingly, a dramatic growth of HIV over the past decade (>250%) has been noted in Eastern Europe and Central Asia with >90% of the people affected living in Russia and Ukraine. Statistics report that Latin America and the Caribbean count for 1.5 million and 200000 people living with HIV respectively.⁴³

PREVENTION OF HIV DRUG RESISTANCE

Resistance to HIV drugs is inevitable due to the virus’ high

Number of people receiving antiretroviral therapy in low- and middle-income countries, by region, 2002-2010

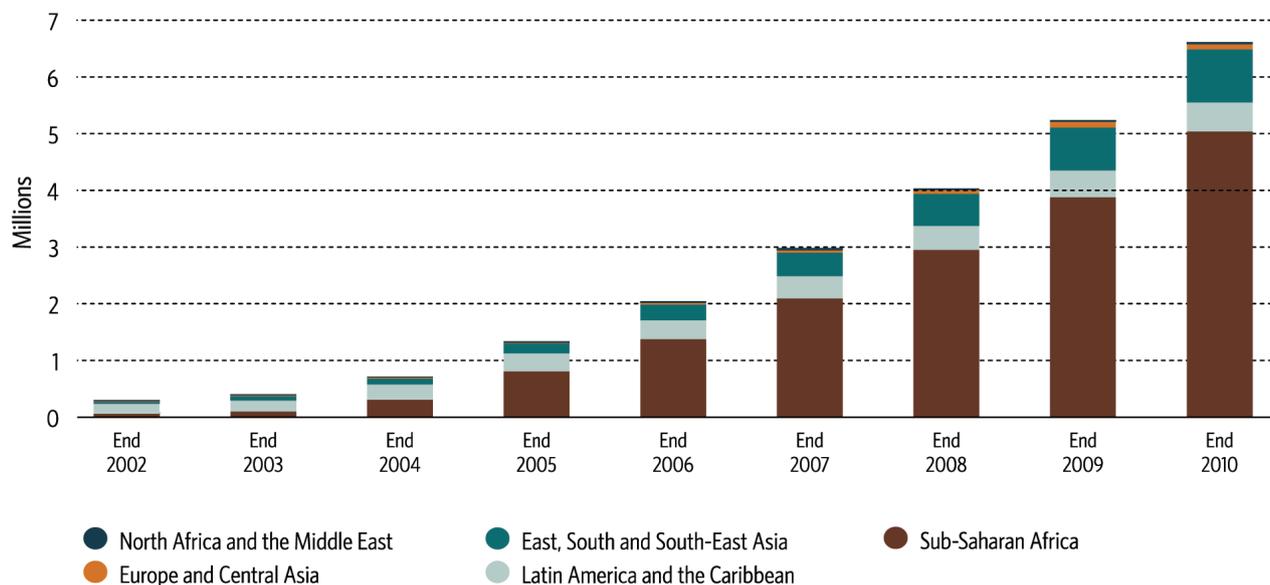


FIGURE 1. WHO Progress Report Summary 2011 (p.18/28)⁴³

mutation rate and recombination and may lead to weakening of the significant gains of antiretroviral treatment. Hence, monitoring of the viral resistance and maintenance of the effectiveness of first- and second-line regimens are of utmost importance.

A recent review of studies conducted in sub-Saharan Africa and India reports a high frequency of resistance mutations among patients failing first-line therapy,⁴⁴ whereas most reports from low- and middle-income countries depict low rates of transmitted resistance.⁴⁵

A global strategy for the prevention and assessment of HIV drug resistance has been implemented by WHO and the Global HIV Drug Resistance Network (HIVResNet), aiming at improving surveillance of HIV drug resistance with regular approaches. WHO recommends that countries should base their strategy for the prevention and assessment of HIV drug resistance on three key considerations: (1) scheduled monitoring of “early warning indicators” of HIV drug resistance, (2) surveys to monitor the emergence of HIV drug resistance in populations receiving antiretroviral therapy, and (3) surveys to evaluate transmitted HIV drug resistance in recently infected populations. By 2010, over 60 countries had implemented one or more elements of the proposed strategy. WHO facilitated achievement of country goals, by approving national, regional and specialized HIV drug resistance testing laboratories and by December 2009, 24 HIV drug resistance testing laboratories had been accredited.⁷

Nevirapine (NVP) has been widely used as single dose prophylaxis at the onset of labor,^{46,47} however even a single dose

frequently induces viral resistance.^{48,49} Aiming at reducing viral resistance as well as the risk of vertical HIV-1 transmission, the 2010 WHO guidelines⁵⁰ for the prevention of mother-to-child transmission (PMTCT), supported by findings of recent studies, recommend use of HAART during pregnancy as well as after delivery.^{51,52}

MOTHERS AND CHILDREN

Mother-to-child transmission (MTCT) remains the major route of HIV infection among children.⁵³ Prevention of mother-to-child transmission (PMTCT) programs, particularly in resource-limited settings, need to be scaled up. Mother-to-child transmission rates in the United States and Europe are below 2% due to wide coverage with HAART.⁵⁴ Unfortunately, in contrast to the developed world, only 45% of HIV-positive women in low and middle income countries received antiretroviral prophylaxis for PMTCT in 2008.⁵³

Uptake of PMTCT services in resource-limited settings can be advanced by utilizing novel options such as integrating PMTCT services into existing maternal and child health structures, addressing information gaps as well as activating the people in charge.⁵⁵

According to 2010 WHO report, HIV services for women and children have expanded in 2009. An estimated 26% of all pregnant women in low- and middle income countries received an HIV test in 2009 compared to 21% in 2008, and 53% of pregnant women living with HIV received antiretroviral drugs to reduce the risk of transmitting HIV to their infants compared to 45% in 2008. Sub-Saharan Africa is the region

which has around 91% of the pregnant women in need of antiretroviral drugs; the coverage in 2009 was 54%.⁷

In the pediatric population, an increase of 29% of children less than 15 years of age receiving antiretrovirals was noted in 2009 compared with 2008. These children represented an estimated 28% of all children less than 15 years estimated to need treatment in low- and middle-income countries, up from 22% in 2008 and 7% in 2005.⁷ Overall, antiretroviral therapy coverage among children in low- and middle-income countries was lower than that among adults. Moreover, only 15% of children born from HIV positive mothers were tested for HIV within the first two months of life, in 54 reporting countries.⁷

The 2010 revised guidelines on prevention of mother-to-child transmission of HIV propose major changes for earlier antiretroviral therapy for a larger group of HIV-positive pregnant women (CD4 350 or stage 3 or 4 disease). In addition, the revised guidelines now suggest the provision of antiretrovirals to the mother or child to reduce the risk of HIV transmission during breastfeeding wherever this is judged to be the safest feeding option. Updated pediatric antiretroviral treatment guidelines now advise that all HIV-positive children less than 24 months of age should be started on antiretroviral therapy and that children older than 24 months of age must be initiated on treatment depending on age-specific CD4 cell count thresholds.⁷

Greater efforts are needed to scale up early testing of HIV-exposed infants and further incorporate HIV interventions with services for maternal, newborn and child health.

HIV RELATED TUBERCULOSIS (TB)

HIV-related TB remains an important universal challenge. In 2008, 1.4 million out of 9.4 million people living with TB worldwide were co-infected with HIV. Statistics report that 26% of deaths in people with HIV can be attributed to TB.⁷ Data show that 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. The majority of people living with HIV and TB in the world are encountered in Sub-Saharan Africa.⁵⁶

A total of 58 countries reported at least one case of extensively drug-resistant TB in 2008, with Eastern Europe and Central Asia being the regions more severely affected by multidrug-resistant TB. Difficulties and delays in diagnosis, lack of access to antiretroviral treatment and complications of concurrent treatment for both conditions, as well as inadequate TB infection control measures, all account for possible explanations for the fact that people living with HIV are at higher risk for drug-resistant forms of TB.^{57,58}

Various forms of integrated HIV and TB services have been applied in several countries with promising results. Scientific studies support that antiretroviral therapy can reduce

the incidence of TB, and may diminish morbidity and mortality from TB. Antiretroviral therapy has been characteristically shown to reduce TB incidence by up to 90% at the individual level and by 60% at the population level.⁵⁹ Every person with symptoms and signs of TB and every patient with confirmed TB should therefore be tested for HIV.

INTERVENTIONS FOR HIV PREVENTION

Maximizing the health sector's contribution to HIV prevention is vital and includes interventions meant for people regardless of HIV status (presumed HIV-negative) and for people living with HIV. A set of specific interventions such as counseling on safer sex, enabling people to be informed about their HIV status and educating on transmission prevention, have been proposed for most vulnerable populations such as injecting drug users, men who have sex with men, transgender persons, sex workers, prisoners, pregnant women, infected mothers and health-care workers.⁶⁰

Male circumcision is suggested by WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS) as an additional intervention to reduce the risk of heterosexual transmission of HIV to men. A reduction in HIV transmission among men that were circumcised has been reported by clinical trials.⁶¹⁻⁶³ Circumcision has also been reported to reduce the risk of HIV-1 male to female transmission and to decrease the incidence of multiple infections due to high-risk human papilloma virus (HPV).

Finally, the rapid identification and treatment of sexually transmitted infections is considered to be a key element in controlling the spread of HIV as sexually transmitted infections synergistically increase the risk of HIV transmission. Availability, safety and accessibility of blood and blood products have also been an issue of concern. As proposed by WHO, all activities related to blood collection, testing, processing, storage and distribution should be coordinated at national level through an appropriate legal outline.⁷

New biomedical prevention technologies, such as microbicides, and pre-exposure as well as post-exposure prophylaxis (PEP) with antiretroviral drugs and vaccines, may expand considerably the contribution to HIV prevention. Interestingly, a tenofovir (TDF)-containing vaginal microbicide was found by the Centre for the AIDS Program of Research in South Africa (CAPRISA) to have a statistically significant protective effect against HIV.⁶⁴

Substantial progress has been made in establishing prevention services in many countries. In 2008 however, the number of new infections was still bigger than the number of people started on treatment. This emphasizes the importance of further expanding prevention measures.⁷ Studies referring to serodiscordant couples in Africa, report that strategic use of pre-exposure prophylaxis and antiretroviral therapy reduce HIV-1 transmission in a cost – effective way.^{65,66}

OUTCOMES OF SCALING UP ANTIRETROVIRAL TREATMENT

Surveillance and evaluation of procedures and outcomes are needed in the application of antiretroviral therapy scaling up, as they provide a more adequate understanding on whether programmatic responses are appropriate or not and lead to implementation of changes whenever necessary. Countries all around the world are continuously improving the monitoring and reporting of program retention on antiretroviral therapy. Fox and Rosen report an increased rate of retention (70% - 77% at 24 months and 65% - 72% at 36 months), in patients living in Sub-Saharan Africa. This improvement could lead to a change in the criteria for initiation of antiretroviral therapy, as initiation of antiretrovirals at a high CD4 cell count has been associated with lower mortality and improved treatment outcomes.⁶⁷

Patients diagnosed as HIV positive however, may not start therapy or may start after having reached eligibility levels. Hence, it is very important apart from improving retention, to pay attention to the attrition of patients in HIV care before initiation of antiretroviral therapy.⁶⁸ Evaluation of the impact of antiretroviral therapy on mortality is critical to guarantee the continued political commitment necessary to sustain a lifelong intervention. A systematic analysis of worldwide mortality among adults aged 15–59 years from 1970 to 2010 showed that mortality increased considerably in sub-Saharan Africa in the late 1980s and began to decline since 2005, a trend that coincides with an increase in access to antiretroviral treatment.^{69,70}

Advancing the scale up of antiretroviral therapy has also variably benefited other health-care services. In high income countries an impact of antiretrovirals on reducing morbidity and use of hospital services has been documented.⁷¹ Moreover, a reduction in the burden of care placed on overwhelmed health care systems and a decrease in mortality among health care workers is noted as a result of antiretroviral therapy application in countries highly affected by the epidemic.⁷²

CONCLUSIONS

Over the past 10 years, a number of key strategies have been identified to support scale up of HIV treatment, improve quality of care, and reduce costs. Although many challenges are ahead, the fact is that millions of people are alive today as a result of antiretroviral therapy.

Integrating services and strategies can improve equity, access and coverage and may also improve the quality and efficiency of care. In order to carry out these plans, HIV programs must be executed within a primary health-care framework capable of providing efficient services that address multiple patient needs through continuous care. These include services for maternal and child health, management of tuberculosis and sexually transmitted infections. Strong actions are required to

reduce HIV transmission and to meet the needs of groups at higher risk for HIV infection. Focused efforts are needed to remove punitive laws and create enabling legal environments that address the human rights violations currently blocking effective AIDS responses. The involvement of communities in program management is necessary in order to ensure the adequacy of interventions delivered.

The schedule of the global HIV response remains undoubtedly incomplete. Every day, thousands of people are still being infected and dying due to lack of access to prevention, treatment and care. The sooner high-quality services are scaled up, the larger will be the social and economic gains from fewer infections, lower mortality and better quality of life for those infected. The strengthening of the health care systems is essential to guarantee individuals a life-long therapy even in the rural areas where the majority of people in need of treatment live. Reducing inequity is a global responsibility. The international community has an obligation to mobilize resources to support the low-income nations of the world and the civil society has the duty to ensure that scientific, social and political leaders fulfill their commitments on a local, regional and global basis.

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HIGHLY ACTIVE ANTIRETROVIRAL THERAPY – CURRENT STATUS

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